TITLE OF THE INVENTION

BIARYL SUBSTITUTED 6-MEMBERED HETEROCYLES AS SODIUM CHANNEL BLOCKERS

FIELD OF THE INVENTION

The present invention is directed to a series of biaryl substituted 6-membered heterocyclic compounds. In particular, this invention is directed to biaryl substituted 6-membered pyridine, pyrimidine and pyrazine compounds that are sodium channel blockers useful for the treatment of chronic and neuropathic pain. The compounds of the present invention are also useful for the treatment of other conditions, including, for example, central nervous system (CNS) disorders such as epilepsy, manic depression, bipolar disorder, anxiety, depression and diabetic neuropathy.

BACKGROUND OF THE INVENTION

Voltage-gated ion channels allow electrically excitable cells to generate and propagate action potentials and therefore are crucial for nerve and muscle function. Sodium channels play a special role by mediating rapid depolarization, which constitutes the rising phase of the action potential and in turn activates voltage-gated calcium and potassium channels. Voltage-gated sodium channels represent a multigene family. Nine sodium channel subtypes have been cloned and functionally expressed to date. [Clare, J. J., Tate, S. N., Nobbs, M. & Romanos, M. A. Voltage-gated sodium channels as therapeutic targets. *Drug Discovery Today* **5**, 506-520 (2000)]. They are differentially expressed throughout muscle and nerve tissues and show distinct biophysical properties. All voltage-gated sodium channels are characterized by a high degree of selectivity for sodium over other ions and by their voltage-dependent gating. [Catterall, W. A. Structure and function of voltage-gated sodium and calcium channels. *Current Opinion in Neurobiology* **1**, 5-13 (1991)]. At negative or hyperpolarized membrane potentials, sodium channels are closed. Following membrane depolarization, sodium channels open rapidly and then inactivate. Sodium channels only conduct currents in the open state and, once inactivated, have to return to the resting state, favored by membrane hyperpolarization, before they can reopen. Different sodium channel subtypes vary in the voltage range over which they activate and inactivate as well as in their activation and inactivation kinetics.

Sodium channels are the target of a diverse array of pharmacological agents, including neurotoxins, antiarrhythmics, anticonvulsants and local anesthetics. [Clare, J. J., Tate, S. N., Nobbs, M. & Romanos, M. A. Voltage-gated sodium channels as therapeutic targets. *Drug*

Discovery Today **5**, 506-520 (2000)]. Several regions in the sodium channel secondary structure are involved in interactions with these blockers and most are highly conserved. Indeed, most sodium channel blockers known to date interact with similar potency with all channel subtypes. Nevertheless, it has been possible to produce sodium channel blockers with therapeutic selectivity and a sufficient therapeutic window for the treatment of epilepsy (e.g. lamotrigine, phenytoin and carbamazepine) and certain cardiac arrhythmias (e.g. lignocaine, tocainide and mexiletine).

It is well known that the voltage-gated Na^+ channels in nerves play a critical role in neuropathic pain. Injuries of the peripheral nervous system often result in neuropathic pain persisting long after the initial injury resolves. Examples of neuropathic pain include, but are not limited to, postherpetic neuralgia, trigeminal neuralgia, diabetic neuropathy, chronic lower back pain, phantom limb pain, pain resulting from cancer and chemotherapy, chronic pelvic pain, complex regional pain syndrome and related neuralgias. It has been shown in human patients as well as in animal models of neuropathic pain, that damage to primary afferent sensory neurons can lead to neuroma formation and spontaneous activity, as well as evoked activity in response to normally innocuous stimuli. [Carter, G.T. and B.S. Galer, *Advances in the management of neuropathic pain.* Physical Medicine and Rehabilitation Clinics of North America, 2001. **12**(2): p. 447-459]. The ectopic activity of normally silent sensory neurons is thought to contribute to the generation and maintenance of neuropathic pain. Neuropathic pain is generally assumed to be associated with an increase in sodium channel activity in the injured nerve. [Baker, M.D. and J.N. Wood, *Involvement of Na channels in pain pathways.* TRENDS in Pharmacological Sciences, 2001. **22**(1): p. 27-31].

Indeed, in rat models of peripheral nerve injury, ectopic activity in the injured nerve corresponds to the behavioral signs of pain. In these models, intravenous application of the sodium channel blocker and local anesthetic lidocaine can suppress the ectopic activity and reverse the tactile allodynia at concentrations that do not affect general behavior and motor function. [Mao, J. and L.L. Chen, *Systemic lidocaine for neuropathic pain relief.* Pain, 2000. **87**: p. 7-17]. These effective concentrations were similar to concentrations shown to be clinically efficacious in humans. [Tanelian, D.L. and W.G. Brose, *Neuropathic pain can be relieved by drugs that are use-dependent sodium channel blockers: lidocaine, carbamazepine and mexiletine.* Anesthesiology, 1991. **74**(5): p. 949-951]. In a placebo-controlled study, continuous infusion of lidocaine caused reduced pain scores in patients with peripheral nerve injury, and in a separate study, intravenous lidocaine reduced pain intensity associated with postherpetic neuralgia (PHN). [Mao, J. and L.L. Chen, *Systemic lidocaine for neuropathic pain relief.* Pain,

2000. **87**: p. 7-17. Anger, T., et al., *Medicinal chemistry of neuronal voltage-gated sodium channel blockers.* Journal of Medicinal Chemistry, 2001. **44**(2): p. 115-137]. Lidoderm®, lidocaine applied in the form of a dermal patch, is currently the only FDA approved treatment for PHN. [Devers, A. and B.S. Galer, *Topical lidocaine patch relieves a variety of neuropathic pain conditions: an open-label study.* Clinical Journal of Pain, 2000. **16**(3): p. 205-208].

In addition to neuropathic pain, sodium channel blockers have clinical uses in the treatment of epilepsy and cardiac arrhythmias. Recent evidence from animal models suggests that sodium channel blockers may also be useful for neuroprotection under ischaemic conditions caused by stroke or neural trauma and in patients with multiple sclerosis (MS). [Clare, J. J. *et. al.* And Anger, T. *et. al.*].

International Patent Publication WO 00/57877 describes aryl substituted pyrazoles, imidazoles, oxazoles, thiazoles, and pyrroles and their uses as sodium channel blockers. International Patent Publication WO 01/68612 describes aryl substituted pyridines, pyrimidines, pyrazines and triazines and their uses as sodium channel blockers. International Patent Publication WO 99/32462 describes triazine compounds for the treatment for CNS disorders. However, there remains a need for novel compounds and compositions that therapeutically block neuronal sodium channels with less side effects and higher potency than currently known compounds.

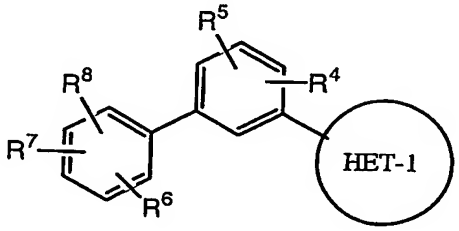
SUMMARY OF THE INVENTION

The present invention is directed to biaryl substituted 6-membered pyridine, pyrimidine and pyrazine compounds which are sodium channel blockers useful for the treatment of chronic and neuropathic pain. The compounds of the present invention are also useful for the treatment of other conditions, including CNS disorders such as anxiety, depression, epilepsy, manic depression and bipolar disorder. This invention provides pharmaceutical compositions comprising a compound of the present invention, either alone, or in combination with one or more therapeutically active compounds, and a pharmaceutically acceptable carrier.

This invention further comprises methods for the treatment of conditions associated with, or resulting from, sodium channel activity, such as acute pain, chronic pain, visceral pain, inflammatory pain, neuropathic pain and disorders of the CNS including, but not limited to, anxiety, depression, epilepsy, manic depression and bipolar disorder.

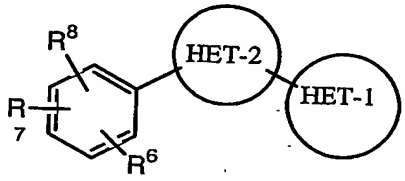
DETAILED DESCRIPTION OF THE INVENTION

The compounds described in the present invention are represented by Formula (I) or (II):



(I)

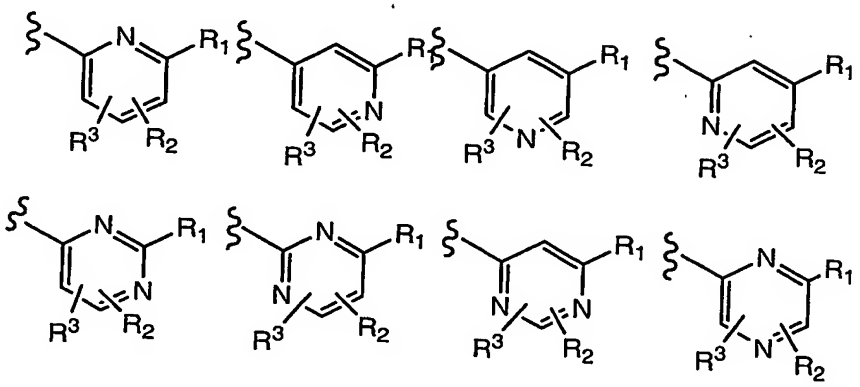
or



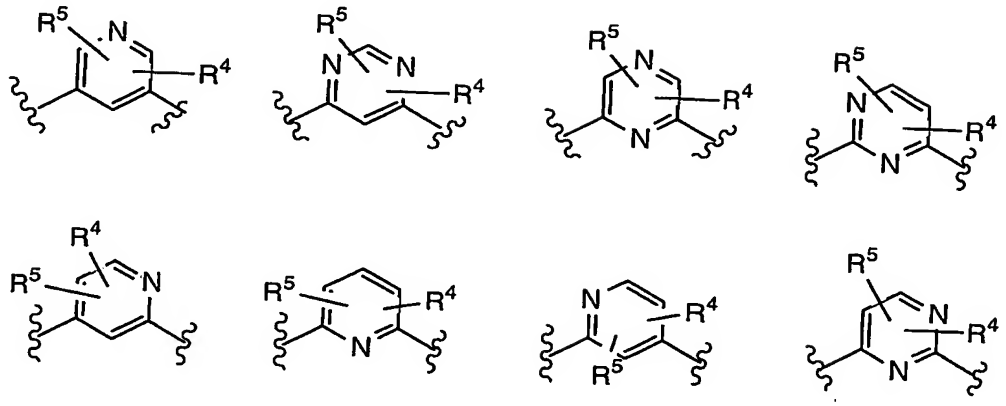
(II)

or a pharmaceutically acceptable salt thereof, wherein

HET-1 is one of the following heterocycles:



HET-2 is one of the following heterocycles:



R^1 is

(a) H;

(b) C_1-C_6-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl,C_3-C_6-cycloalkyl, or C_1-C_4-alkyl-[C_3-C_6-cycloalkyl], any of which is optionally substituted with one or more of the following substituents: F, CF_3, OH, O-(C_1-C_4)alkyl, S(O)$_{0-2}$-(C_1-C_4)alkyl, O-CONR^{a}R^b, NR^{a}R^b, N(R^a)CONR^{a}R^b, COO-(C_1-C_4)alkyl, COOH, CN, CONR^{a}R^b, SO_2NR^{a}R^b, N(R^a)SO_2NR^{a}R^b, -C(=NH)NH_2, tetrazolyl, triazolyl, imidazolyl, oxazolyl, oxadiazolyl, isooxazolyl, thiazolyl, furyl, thienyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyrazinyl, phenyl, piperidinyl, morpholinyl, pyrrolidinyl or piperazinyl;

(c) -O-C_1-C_6-alkyl, -O-C_3-C_6-cycloalkyl, -S-C_1-C_6-alkyl or -S-C_3-C_6-cycloalkyl, any of which is optionally substituted with one or more of the following substituents: F, CF_3, OH, O-(C_1-C_4)alkyl, S(O)$_{0-2}$-(C_1-C_4)alkyl, O-CONR^{a}R^b, NR^{a}R^b, N(R^a)CONR^{a}R^b, COO-(C_1-C_4)alkyl, COOH, CN, CONR^{a}R^b, SO_2NR^{a}R^b, N(R^a)SO_2NR^{a}R^b, -C(=NH)NH_2, tetrazolyl, triazolyl, imidazolyl, oxazolyl, oxadiazolyl, isooxazolyl, thiazolyl, furyl, thienyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyrazinyl, phenyl, piperidinyl, morpholinyl, pyrrolidinyl or piperazinyl;

(d) -C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl, or -O-C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl;

(e) -OH;

(f) -O-aryl, or –O-C_1-C_4-alkyl-aryl, wherein aryl is phenyl, pyridyl, pyrimidinyl, furyl, thienyl, pyrrolyl, triazolyl, pyrazolyl, thiazolyl, isoxazolyl, oxazolyl, or oxadiazolyl, any aryl of which is optionally substituted with 1-3 substituents selected from i) F, Cl, Br, I, ii) -CN, iii) -NO_2, iv) –C(=O)(R^a), v) -OR^a, vi) -NR^{a}R^b, vii) -C_{0-4}alkyl-CO-OR^a, viii) -(C_{0-4}alkyl)-NH-CO-OR^a, ix) -(C_{0-4}alkyl)-CO-N(R^a)(R^b), x) -S(O)$_{0-2}$R^a, xi) -SO_2N(R^a)(R^b), xii) -NR^aSO_2R^a, xiii) -C_{1-10}alkyl, and xiv) -C_{1-10}alkyl, wherein one or more of the alkyl carbons can be

replaced by a -NR^a-, -O-, -$S(O)_{1-2}$-, -O-C(O)-, -C(O)-O-, -C(O)-$N(R^a)$-, -$N(R^a)$-C(O)-, -$N(R^a)$-C(O)-$N(R^a)$-, -C(O)-, -CH(OH)-, -C=C-, or -C≡C- ;

(g) -$OCON(R^a)(R^b)$, or -$OSO_2N(R^a)(R^b)$;

(h) -SH, or -$SCON(R^a)(R^b)$;

(i) NO_2;

(j) NR^aR^b, -$N(COR^a)R^b$, -$N(SO_2R^a)R^b$, -$N(R^a)CON(R^a)_2$, -$N(R^a)CONH_2$, -$N(OR^a)CONR^aR^b$, -$N(R^a)CON(R^a)_2$, or -$N(R^a)SO_2N(R^a)_2$;

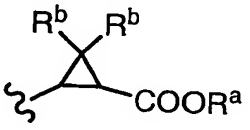
(k) -$CH(OR^a)R^a$, -$C(OR^b)CF_3$, -$CH(NHR^b)R^a$, -$C(=O)R^a$, $C(=O)CF_3$, -$SOCH_3$, -SO_2CH_3, -$N(R^a)SO_2R^a$, $COOR^a$, CN, $CONR^aR^b$, -$COCONR^aR^b$, -$SO_2NR^aR^b$, -CH_2O-$SO_2NR^aR^b$, $SO_2N(R^a)OR^a$, -$C(=NH)NH_2$, -CR^a=N-OR^a, $CH=CHCONR^aR^b$, $CONR^a$, $CONHR^a$;

(l) -$CONR^a(CH_2)_{0-2}C(R^a)(R^b)(CH_2)_{0-2}CONR^aR^b$;

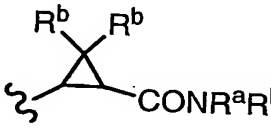
(m) tetrazolyl, tetrazolinonyl, triazolyl, triazolinonyl, imidazolyl, imidozolonyl, oxazolyl, oxadiazolyl, isooxazolyl, thiazolyl, furyl, thienyl, pyrazolyl, pyrazolonyl, pyrrolyl, pyridyl, pyrimidinyl, pyrazinyl, or phenyl, any of which is optionally substituted with 1-3 substituents selected from i) F, Cl, Br, I, ii) -CN, iii) -NO_2, iv) -$C(=O)R^a$, v) C_1-C_6-alkyl , vi) -O-R^a, vii) -NR^aR^b , viii) - C_0-C_4-alkyl -CO-O R^a, ix) -(C_0-C_4-alkyl)-NH-CO-OR^a, x) -(C_0-C_4-alkyl)-CO-NR^a R^b, xi) –$S(O)_{0-2}R^a$, xii) -$SO_2NR^aR^b$, xiii) -$NHSO_2R^a$, xiv) –C_1-C_4-perfluoroalkyl, and xv) –O-C_1-C_4-perfluoroalkyl;

(n) -$C(R^a)$=$C(R^b)$-$COOR^a$, or -$C(R^a)$=$C(R^b)$-$CONR^aR^b$;

(o)



or



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(p) piperidin-1-yl, morpholin-4-yl, pyrrolidin-1-yl, piperazin-1-yl or 4-susbstituted piperazin-1-yl, any of which is optionally substituted with 1-3 substituents selected from i) -CN, ii) -C(=O)(R^a), iii) C_1-C_6-alkyl , iv) -OR^a, v) -NR^aR^b, vi) -C_0-C_4-alkyl-CO-OR^a, vii) -(C_0-C_4-alkyl)-NH-CO-OR^a, viii) -(C_0-C_4-alkyl)-$CON(R^a)(R^b)$, ix) -SR^a, x) -$S(O)_{0-2}R^a$, xi) -$SO_2N(R^a)(R^b)$, xii) -$NR^aSO_2R^a$ xiii) -C_1-C_4-perfluoroalkyl and xiv) -O-C_1-C_4-perfluoroalkyl;

R^a is

(a) H;

(b) C_1-C_4-alkyl, optionally substituted with one or more of the following substituents: F, CF_3, OH, O-(C_1-C_4)alkyl, $S(O)_{0-2}$-(C_1-C_4)alkyl, -$OCONH_2$, -OCONH(C_1-C_4alkyl), -OCON(C_1-C_4alkyl)(C_1-C_4alkyl), -OCONH(C_1-C_4alkyl-aryl), -OCON(C_1-C_4alkyl)(C_1-C_4alkyl-aryl), NH_2, NH(C_1-C_4alkyl), N(C_1-C_4alkyl)(C_1-C_4alkyl), NH(C_1-C_4alkyl-aryl), N(C_1-C_4alkyl)(C_1-C_4alkyl-aryl), $NHCONH_2$, NHCONH(C_1-C_4alkyl), NHCONH(C_1-C_4alkyl-aryl), -NHCON(C_1-C_4alkyl)(C_1-C_4alkyl), NHCON(C_1-C_4alkyl)(C_1-C_4alkyl-aryl), N(C_1-C_4alkyl)CON(C_1-C_4alkyl)(C_1-C_4alkyl), N(C_1-C_4alkyl)CON(C_1-C_4alkyl)(C_1-C_4alkyl-aryl), COO-(C_1-C_4-alkyl), COOH, CN, $CONH_2$, CONH(C_1-C_4alkyl), CON(C_1-C_4alkyl)(C_1-C_4alkyl), SO_2NH_2, SO_2NH(C_1-C_4alkyl), SO_2NH(C_1-C_4alkyl-aryl), SO_2N(C_1-C_4alkyl)(C_1-C_4alkyl), $NHSO_2NH_2$, -C(=NH)NH_2, tetrazolyl, triazolyl, imidazolyl, oxazolyl, oxadiazolyl, isooxazolyl, thiazolyl, furyl, thienyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyrazinyl, phenyl, piperidinyl, morpholinyl, pyrrolidinyl or piperazinyl;

(c) C_0-C_4-alkyl-(C_1-C_4)-perfluoroalkyl; or

(d) -C_1-C_4-alkyl-aryl, wherein aryl is phenyl, pyridyl, pyrimidinyl, furyl, thienyl, pyrrolyl, triazolyl, pyrazolyl, thiazolyl, isoxazolyl, oxazolyl, or oxadiazolyl, any aryl of which is optionally substituted with 1-3 substituents selected from i) F, Cl, Br, I, ii) -CN, iii) -NO_2, iv) –C(=O)(C_1-C_4-alkyl), v) -O(C_1-C_4-alkyl), vi) -N(C_1-C_4-alkyl)(C_1-C_4-alkyl), vii) -C_{1-10}alkyl, and viii) -C_{1-10}alkyl,wherein one or more of the alkyl carbons can be replaced by a , - O-, -$S(O)_{1-2}$-, -O-C(O)-, -C(O)-O-, -C(O)-, -CH(OH)-, -C=C-, or -C≡C-;

R^b is

(a) H; or

(b) C_1-C_6-alkyl, optionally substituted with one or more of the following substituents: F, CF_3, OH, O-(C_1-C_4)alkyl, $S(O)_{0-2}$-(C_1-C_4)alkyl, -$OCONH_2$, -OCONH(C_1-C_4alkyl), NH_2, NH, NH(C_1-C_4alkyl), N(C_1-C_4alkyl), N(C_1-C_4alkyl)(C_1-C_4alkyl), $NHCONH_2$, NHCONH(C_1-C_4alkyl), -NHCON(C_1-C_4alkyl)(C_1-C_4alkyl), COO-(C_1-C_4-alkyl), COOH, CN, pyridyl, piperidinyl, pyrimidinyl, piperazinyl, $CONH_2$ or (C_1-C_4alkyl)$CONH_2$; or

R^a and R^b, together with the N to which they are attached, can form a 5- or 6-membered ring which optionally contains a heteroatom selected from N, O, and S, and wherein said ring is optionally substituted with 1-3 substituents selected from i) F, Cl, Br, I, ii) -CN, iii) -NO_2, iv) –C(=O)(R^a), v) -OR^a, vi) -NR^aR^b, vii) -C_{0-4}alkyl-CO-OR^a, viii) -(C_{0-4}alkyl)-NH-CO-OR^a, ix) -(C_{0-4}alkyl)-CO-N(R^a)(R^b), x) -$S(O)_{0-2}R^a$, xi) -$SO_2N(R^a)(R^b)$, xii) -$NR^aSO_2R^a$, xiii) -C_{1-10}alkyl, and xiv) –O-;

R^2 and R^3 each independently is:

(a) H;

(b) - C_1-C_4-alkyl, or -O-C_1-C_4-alkyl;

(c) -C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl, or -O-C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl; or

(d) CN, N R^a R^b, NO_2, F, Cl, Br, I, OH, $OCONR^a$ R^b, $O(C_1$-C_4-alkyl)$CONR^a$ R^b ,-OSO_2NR^a R^b, $COOR^a$, $N(R^a)COR^a$, or $CONR^a$ R^b;

R^4 and R^5 each independently is:

(a) H;

(b) -C_1-C_6-alkyl, -C_2-C_6-alkenyl, -C_2-C_6-alkynyl or -C_3-C_6-cycloalkyl, any of which is optionally substituted with one or more of the following substituents: F, CF_3, -O-$(C_1$-$C_4)$alkyl, CN, -$N(R^a)(R^b)$, -$N(R^a)CO$-$(C_1$-$C_4)$alkyl, $COOR^b$, $CON(R^a)(R^b)$ or phenyl;

(c) -O-C_0-C_6-alkyl, -O-aryl, or -O-C_1-C_4-alkyl-aryl, wherein aryl is phenyl, pyridyl, pyrimidinyl, furyl, thienyl, pyrrolyl, triazolyl, pyrazolyl, thiazolyl, isoxazolyl, oxazolyl, or oxadiazolyl, any aryl of which is optionally substituted with 1-3 substituents selected from i) F, Cl, Br, I, ii) -CN, iii) -NO_2, iv) –C(=O)(R^a), v) -OR^a, vi) -NR^aR^b, vii) -C0-4alkyl-CO-OR^a, viii) -(C0-4alkyl)-NH-CO-OR^a, ix) -(C0-4alkyl)-CO-$N(R^a)(R^b)$, x) -$S(O)_{0-2}R^a$, xi) -$SO_2N(R^a)(R^b)$, xii) -$NR^aSO_2R^a$, xiii) -C1-10alkyl, and xiv) -C1-10alkyl,wherein one or more of the alkyl carbons can be replaced by a -NR^a-, - O-, -$S(O)_{1-2}$-, -O-C(O)-, -C(O)-O-, -C(O)-$N(R^a)$-, -$N(R^a)$-C(O)-, -$N(R^a)$-C(O)-$N(R^a)$-, -C(O)-, -CH(OH)-, -C=C-, or -C≡C-;

(d) -C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl, or -O-C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl; or

(e) CN, NH_2, NO_2, F, Cl, Br, I, OH, $OCON(R^a)(R^b)$ $O(C_1$-C_4-alkyl)$CONR^aR^b$, -$OSO_2N(R^a)(R^b)$, $COOR^b$, $CON(R^a)(R^b)$, or aryl, wherein aryl is phenyl, pyridyl, pyrimidinyl, furyl, thienyl, pyrrolyl, triazolyl, pyrazolyl, thiazolyl, isoxazolyl, oxazolyl, or oxadiazolyl, any aryl of which is optionally substituted with 1-3 substituents selected from i) F, Cl, Br, I, ii) -CN, iii) -NO_2, iv) –C(=O)(R^a), v) -OR^a, vi) -NR^aR^b, vii) -C0-4alkyl-CO-OR^a, viii) -(C0-4alkyl)-NH-CO-OR^a, ix) -(C0-4alkyl)-CO-$N(R^a)(R^b)$, x) -$S(O)_{0-2}R^a$, xi) -$SO_2N(R^a)(R^b)$, xii) -$NR^aSO_2R^a$, xiii) -C1-10alkyl, and xiv) -C1-10alkyl,wherein one or more of the alkyl carbons can be replaced by a -NR^a-, - O-, -$S(O)_{1-2}$-, -O-C(O)-, -C(O)-O-, -C(O)-$N(R^a)$-, -$N(R^a)$-C(O)-, -$N(R^a)$-C(O)-$N(R^a)$-, -C(O)-, -CH(OH)-, -C=C-, or -C≡C; and

R^6, R^7 and R^8 each independently is:

(a) H;

(b) C_1-C_6-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl or C_3-C_6-cycloalkyl, any of which is optionally substituted with one or more of the following substituents: F, CF_3, OH, O-(C_1-C_4)alkyl, $OCON(R^a)(R^b)$, NR^aR^b, $COOR^a$, CN, $CONR^aR^b$, $N(R^a)CONR^aR^b$, $N(R^a)SO_2NR^aR^b$, $SO_2NR^aR^b$, $S(O)_{0-2}(C_1$-C_4-alkyl), $-C(=NH)NH_2$, tetrazolyl, triazolyl, imidazolyl, oxazolyl, oxadiazolyl, isooxazolyl, thiazolyl, furyl, thienyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyrazinyl, phenyl, piperidinyl, morpholinyl, pyrrolidinyl, or piperazinyl;

(c) -O- C_1-C_6-alkyl, -O-C_3-C_6-cycloalkyl, -S-C_1-C_6-alkyl or -S-C_3-C_6-cycloalkyl, any of which is optionally substituted with one or more of the following substituents: F, CF_3, OH, O-(C_1-C_4)alkyl, NH_2, $NH(C_1$-C_4-alkyl), $N(C_1$-C_4-alkyl)$_2$, COOH, CN, $CONH_2$, $CONH(C_1$-C_4-alkyl), $CONH(C_1$-C_4-alkyl)$_2$, SO_2NH_2, $SO_2NH(C_1$-C_4-alkyl), tetrazolyl, triazolyl, imidazolyl, oxazolyl, oxadiazolyl, isooxazolyl, thiazolyl, furyl, thienyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyrazinyl, phenyl, piperidinyl, morpholinyl, pyrrolidinyl, or piperazinyl;

(d) -C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl, or -O-C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl;

(e) -O-aryl, or -O-C_1-C_4-alkyl-aryl, wherein aryl is phenyl, pyridyl, pyrimidinyl, furyl, thienyl, pyrrolyl, triazolyl, pyrazolyl, thiazolyl, isoxazolyl, oxazolyl, or oxadiazolyl, any aryl of which is optionally substituted with 1-3 substituents selected from i) F, Cl, Br, I, ii) -CN, iii) $-NO_2$, iv) $-C(=O)(R^a)$, v) $-OR^a$, vi) $-NR^aR^b$, vii) -C_{0-4}alkyl-CO-OR^a, viii) -(C_{0-4}alkyl)-NH-CO-OR^a, ix) -(C_{0-4}alkyl)-CO-$N(R^a)(R^b)$, x) $-S(O)_{0-2}R^a$, xi) $-SO_2N(R^a)(R^b)$, xii) $-NR^aSO_2R^a$, xiii) -C_{1-10}alkyl, and xiv) -C_{1-10}alkyl,wherein one or more of the alkyl carbons can be replaced by a $-NR^a-$, - O-, $-S(O)_{1-2}-$, -O-C(O)-, -C(O)-O-, $-C(O)-N(R^a)-$, $-N(R^a)-C(O)-$, $-N(R^a)-C(O)-N(R^a)-$, -C(O)-, -CH(OH)-, -C=C-, or -C≡C;

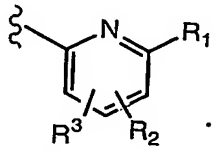
(f) CN, $N(R^a)(R^b)$, NO_2, F, Cl, Br, I, $-OR^a$, $-SR^a$, $-OCON(R^a)(R^b)$, $-OSO_2N(R^a)(R^b)$, $COOR^b$, $CON(R^a)(R^b)$, $-N(R^a)CON(R^a)(R^b)$, $-N(R^a)SO_2N(R^a)(R^b)$, $-C(OR^b)R^a$, $-C(OR^a)CF_3$, $-C(NHR^a)CF_3$, $-C(=O)R^a$, $C(=O)CF_3$, $-SOCH_3$, $-SO_2CH_3$, $-NHSO_2(C_{1-6}$-alkyl), $-NHSO_2$-aryl, $SO_2N(R^a)(R^b)$, $-CH_2OSO_2N(R^a)(R^b)$, $SO_2N(R^b)$-OR^a, $-C(=NH)NH_2$, $-CR_a=N-OR_a$, CH=CH or aryl, wherein aryl is phenyl, pyridyl, pyrimidinyl, furyl, thienyl, pyrrolyl, triazolyl, pyrazolyl, thiazolyl, isoxazolyl, oxazolyl, or oxadiazolyl, any aryl of which is optionally substituted with 1-3 substituents selected from i) F, Cl, Br, I, ii) -CN, iii) $-NO_2$, iv) $-C(=O)(R^a)$, v) $-OR^a$, vi) $-NR^aR^b$, vii) -C_{0-4}alkyl-CO-OR^a, viii) -(C_{0-4}alkyl)-NH-CO-OR^a, ix) -(C_{0-4}alkyl)-CO-$N(R^a)(R^b)$, x) $-S(O)_{0-2}R^a$, xi) $-SO_2N(R^a)(R^b)$, xii) $-NR^aSO_2R^a$, xiii) -C_{1-10}alkyl, and xiv) -C_{1-10}alkyl,wherein one or more of the alkyl carbons can be replaced by a $-NR^a-$, - O-, $-S(O)_{1-2}-$, -O-C(O)-, -C(O)-O-, $-C(O)-N(R^a)-$, $-N(R^a)-C(O)-$, $-N(R^a)-C(O)-N(R^a)-$, -C(O)-, -CH(OH)-, -C=C-, or -C≡C; or

when R^6 and R^7 are present on adjacent carbon atoms, R^6 and R^7, together with the benzene ring to which they are attached, can form a bicyclic aromatic ring selected from naphthyl, indolyl, quinolinyl, isoquinolinyl, quinoxalinyl. benzofuryl, benzothienyl, benzoxazolyl, benzothiazolyl, and benzimidazolyl, any of which is optionally substituted with 1-4 independent substituents selected from i) halogen, ii) -CN, iii) $-NO_2$, iv) –CHO, v) -O-C_{1-4}alkyl, vi) -N(C_{0-4}alkyl)(C_{0-4}alkyl), vii) -C_{0-4}alkyl-CO-O(C_{0-4}alkyl), viii) -(C_{0-4}alkyl)-NH-CO-O(C_{0-4}alkyl), ix) -(C_{0-4}alkyl)-CO-N(C_{0-4}alkyl)(C_{0-4}alkyl), x) -S(C_{0-4}alkyl), xi) -S(O)(C_{1-4}alkyl), xii) $-SO_2$(C_{0-4}alkyl), xiii) $-SO_2$N(C_{0-4}alkyl)(C_{0-4}alkyl), xiv) $-NHSO_2$(C_{0-4}alkyl)(C_{0-4}alkyl), xv) $-C_{1-10}$alkyl and xvi) $-C_{1-10}$alkyl in which one or more of the carbons can be replaced by a -N(C_{0-6}alkyl)-, -O-, $-S(O)_{1-2}$-, -O-C(O)-, -C(O)-O-, -C(O)-N(C_{0-6}alkyl)-, -N(C_{0-6}alkyl)-C(O)-, -N(C_{0-6}alkyl)-C(O)-N(C_{0-6}alkyl)-, -C(O)-, -CH(OH), -C=C-, or -C≡C-.

In one aspect, the present invention provides a compound described by the chemical Formula (I), or a pharmaceutically acceptable salt thereof.

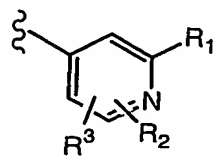
In an embodiment of this one aspect, the present invention provides a compound described by the chemical Formula (I), or a pharmaceutically acceptable salt thereof, wherein

HET-1 is



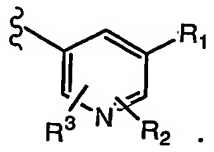
In another embodiment of this one aspect, the present invention provides a compound described by the chemical Formula (I), or a pharmaceutically acceptable salt thereof, wherein

HET-1 is



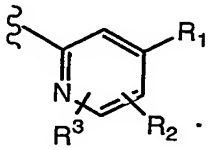
In a further embodiment of this one aspect, the present invention provides a compound described by the chemical Formula (I), or a pharmaceutically acceptable salt thereof, wherein

HET-1 is



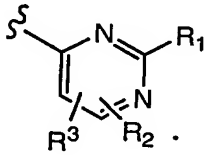
In yet another embodiment of this one aspect, the present invention provides a compound described by the chemical Formula (I), or a pharmaceutically acceptable salt thereof, wherein

HET-1 is



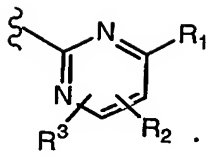
In a still further embodiment of this one aspect, the present invention provides a compound described by the chemical Formula (I), or a pharmaceutically acceptable salt thereof, wherein

HET-1 is



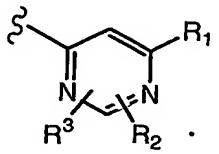
In a still other embodiment of this one aspect, the present invention provides a compound described by the chemical Formula (I), or a pharmaceutically acceptable salt thereof, wherein

HET-1 is



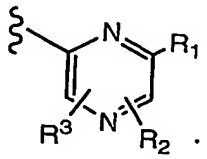
In yet still another embodiment of this one aspect, the present invention provides a compound described by the chemical Formula (I), or a pharmaceutically acceptable salt thereof, wherein

HET-1 is



In a yet further embodiment of this one aspect, the present invention provides a compound described by the chemical Formula (I), or a pharmaceutically acceptable salt thereof, wherein

HET-1 is



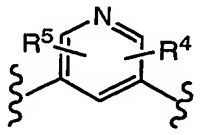
In a yet still further embodiment of this one aspect, the present invention provides a compound described by the chemical Formula (I), or a pharmaceutically acceptable salt thereof, wherein

R^6 is other than H and is attached at the ortho position.

In a second aspect, the present invention provides a compound described by the chemical Formula (II), or a pharmaceutically acceptable salt thereof.

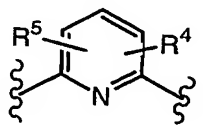
In an embodiment of this second aspect, the present invention provides a compound described by the chemical Formula (II), or a pharmaceutically acceptable salt thereof, wherein

HET-2 is



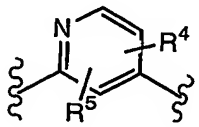
In another embodiment of this second aspect, the present invention provides a compound described by the chemical Formula (II), or a pharmaceutically acceptable salt thereof, wherein

HET-2 is



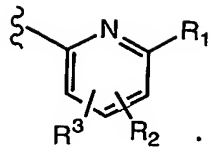
In a further embodiment of this second aspect, the present invention provides a compound described by the chemical Formula (II), or a pharmaceutically acceptable salt thereof, wherein

HET-2 is



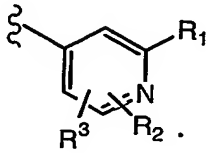
In a still further embodiment of this second aspect, the present invention provides a compound described by the chemical Formula (II), or a pharmaceutically acceptable salt thereof, wherein

HET-1 is



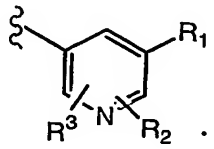
In yet another embodiment of this second aspect, the present invention provides a compound represented by the Formula (II), or a pharmaceutically acceptable salt thereof, wherein

HET-1 is



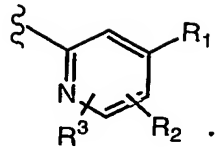
In an other embodiment of this second aspect, the present invention provides a compound represented by the Formula (II), or a pharmaceutically acceptable salt thereof, wherein

HET-1 is



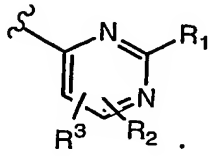
In a still other embodiment of this second aspect, the present invention provides a compound represented by the Formula (II), or a pharmaceutically acceptable salt thereof, wherein

HET-1 is



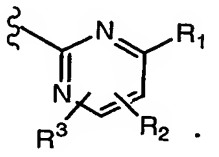
In yet still another embodiment of this second aspect, the present invention provides a compound represented by the Formula (II), or a pharmaceutically acceptable salt thereof, wherein

HET-1 is



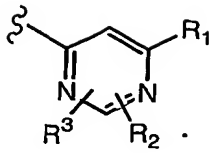
In a yet further embodiment of this second aspect, the present invention provides a compound represented by the Formula (II), or a pharmaceutically acceptable salt thereof, wherein

HET-1 is



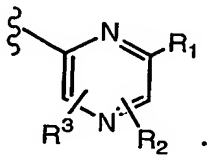
In a yet still further embodiment of this second aspect, the present invention provides a compound represented by the Formula (I), or a pharmaceutically acceptable salt thereof, wherein

HET-1 is



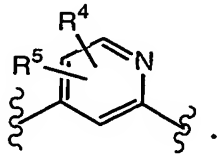
In an additional embodiment of this second aspect, the present invention provides a compound represented by the Formula (II), or a pharmaceutically acceptable salt thereof, wherein

HET-1 is



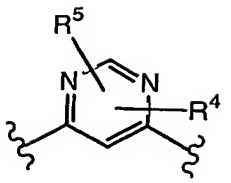
In a still additional embodiment of this second aspect, the present invention provides a compound represented by the Formula (II), or a pharmaceutically acceptable salt thereof, wherein

HET-2 is



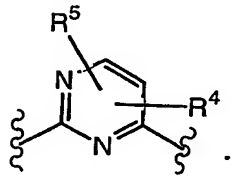
In a yet additional embodiment of this second aspect, the present invention provides a compound represented by the Formula (II), or a pharmaceutically acceptable salt thereof, wherein

HET-2 is



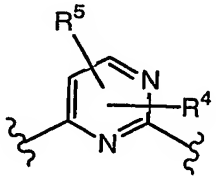
In a further additional embodiment of this second aspect, the present invention provides a compound represented by the Formula (II), or a pharmaceutically acceptable salt thereof, wherein

HET-2 is



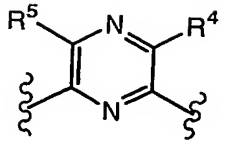
In a yet still other embodiment of this second aspect, the present invention provides a compound represented by the Formula (II), or a pharmaceutically acceptable salt thereof, wherein

HET-2 is



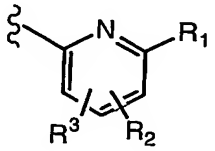
In a yet still another embodiment of this second aspect, the present invention provides a compound represented by the Formula (II), or a pharmaceutically acceptable salt thereof, wherein

HET-2 is



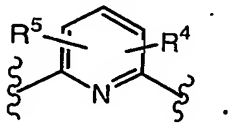
In a third aspect, the present invention provides a compound represented by the Formula (II), or a pharmaceutically acceptable salt thereof, wherein

HET-1 is



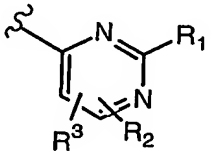
and

HET-2 is



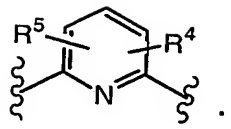
In a fourth aspect, the present invention provides a compound represented by the Formula (II), or a pharmaceutically acceptable salt thereof, wherein

HET-1 is



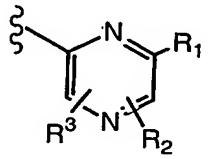
and

HET-2 is



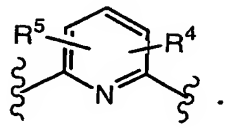
In a fifth aspect, the present invention provides a compound represented by the Formula (II), or a pharmaceutically acceptable salt thereof, wherein

HET-1is



and

HET-2 is



As used herein, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkoxy, alkanoyl, alkenyl, and alkynyl means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, and heptyl. "Alkenyl," "alkynyl" and other like terms include carbon chains containing at least one unsaturated C-C bond.

The term "cycloalkyl" means carbocycles containing no heteroatoms, and includes mono-, bi- and tricyclic saturated carbocycles, as well as fused ring systems. Such fused ring systems can include one ring that is partially or fully unsaturated such as a benzene ring to form fused ring systems such as benzofused carbocycles. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthalene, adamantane, indanyl, indenyl, fluorenyl, and 1,2,3,4-

tetrahydronaphalene. Similarly, "cycloalkenyl" means carbocycles containing no heteroatoms and at least one non-aromatic C-C double bond, and include mono-, bi- and tricyclic partially saturated carbocycles, as well as benzofused cycloalkenes. Examples of cycloalkenyl include cyclohexenyl, and indenyl.

The term "aryl" includes, but is not limited to, an aromatic substituent that is a single ring or multiple rings fused together. When formed of multiple rings, at least one of the constituent rings is aromatic. The term "aryl", unless specifically noted otherwise, also includes heteroaryls, and thus includes stable 5- to 7-membered monocyclic and stable 9- to 10-membered fused bicyclic heterocyclic ring systems that consist of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O and S, wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. Suitable aryl groups include phenyl, naphthyl, pyridyl, pyrimidinyl, furyl, thienyl, pyrrolyl, triazolyl, pyrazolyl, thiazolyl, isoxazolyl, oxazolyl, and oxadiazolyl.

The term "cycloalkyloxy," unless specifically stated otherwise, includes a cycloalkyl group connected by a short C_{1-2}alkyl to the oxy connecting atom.

The term "C_{0-6}alkyl" includes alkyls containing 6, 5, 4, 3, 2, 1, or no carbon atoms. An alkyl with no carbon atoms is a hydrogen atom substituent when the alkyl is a terminal group and is a direct bond when the alkyl is a bridging group.

The term "hetero," unless specifically stated otherwise, includes one or more O, S, or N atoms. For example, heterocycloalkyl and heteroaryl include ring systems that contain one or more O, S, or N atoms in the ring, including mixtures of such atoms. The hetero atoms replace ring carbon atoms. Thus, for example, a heterocycloC_5alkyl is a five-member ring containing from 4 to no carbon atoms. Examples of heteroaryls include pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinoxalinyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, benzoxazolyl, isoxazolyl, thiazolyl, benzothiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, and tetrazolyl. Examples of heterocycloalkyls include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, imidazolinyl, pyrolidin-2-one, piperidin-2-one, and thiomorpholinyl.

The term "heteroC_{0-4}alkyl" means a heteroalkyl containing 3, 2, 1, or no carbon atoms. However, at least one heteroatom must be present. Thus, as an example, a heteroC_{0-4}alkyl having no carbon atoms but one N atom would be a -NH– if a bridging group and a $-NH_2$ if a terminal group. Analogous bridging or terminal groups are clear for an O or S heteroatom.

The term "amine," unless specifically stated otherwise, includes primary, secondary and tertiary amines.

The term "carbonyl," unless specifically stated otherwise, includes a C_{0-6}alkyl substituent group when the carbonyl is terminal.

The term "halogen" includes fluorine, chlorine, bromine and iodine atoms.

The term "optionally substituted" is intended to include both substituted and unsubstituted. Thus, for example, optionally substituted aryl could represent a pentafluorophenyl or a phenyl ring. Further, optionally substituted multiple moieties such as, for example, alkylaryl are intended to mean that the alkyl and the aryl groups are optionally substituted. If only one of the multiple moieties is optionally substituted then it will be specifically recited such as "an alkylaryl, the aryl optionally substituted with halogen or hydroxyl."

Compounds described herein may contain one or more double bonds and may thus give rise to cis/trans isomers as well as other conformational isomers. The present invention includes all such possible isomers as well as mixtures of such isomers unless specifically stated otherwise.

Compounds described herein can contain one or more asymmetric centers and may thus give rise to diastereoisomers and optical isomers. The present invention includes all such possible diastereoisomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above chemical Formulas are shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of the chemical Formulas and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-

toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, and tromethamine..

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like.

The pharmaceutical compositions of the present invention comprise a compound represented by Formula I or II (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier, and optionally one or more additional therapeutic agents or adjuvants. Such additional therapeutic agents can include, for example, i) opiate agonists or antagonists, ii) calcium channel antagonists, iii) 5HT receptor agonists or antagonists iv) sodium channel antagonists, v) NMDA receptor agonists or antagonists, vi) COX-2 selective inhibitors, vii) NK1 antagonists, viii) non-steroidal anti-inflammatory drugs ("NSAID"), ix) selective serotonin reuptake inhibitors ("SSRI") and/or selective serotonin and norepinephrine reuptake inhibitors ("SSNRI"), x) tricyclic antidepressant drugs, xi) norepinephrine modulators, xii) lithium, xiii) valproate, and xiv) neurontin (gabapentin). The instant compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

The present compounds and compositions are useful for the treatment of chronic, visceral, inflammatory and neuropathic pain syndromes. They are useful for the treatment of pain resulting from traumatic nerve injury, nerve compression or entrapment, postherpetic neuralgia, trigeminal neuralgia, and diabetic neuropathy. The present compounds and compositions are also useful for the treatment of chronic lower back pain, phantom limb pain,

chronic pelvic pain, neuroma pain, complex regional pain syndrome, chronic arthritic pain and related neuralgias, and pain associated with cancer, chemotherapy, HIV and HIV treatment-induced neuropathy. Compounds of this invention may also be utilized as local anesthetics. Compounds of this invention are useful for the treatment of irritable bowel syndrome and related disorders, as well as Crohns disease.

The instant compounds have clinical uses for the treatment of epilepsy and partial and generalized tonic seizures. They are also useful for neuroprotection under ischaemic conditions caused by stroke or neural trauma and for treating multiple sclerosis. The present compounds are useful for the treatment of tachy-arrhythmias. Additionally, the instant compounds are useful for the treatment of neuropsychiatric disorders, including mood disorders, such as depression or more particularly depressive disorders, for example, single episodic or recurrent major depressive disorders and dysthymic disorders, or bipolar disorders, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder; anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and acute stress disorder, and generalised anxiety disorders;

It will be appreciated that for the treatment of depression or anxiety, a compound of the present invention may be used in conjunction with other anti-depressant or anti-anxiety agents, such as norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), α-adrenoreceptor antagonists, atypical anti-depressants, benzodiazepines, 5-HT_{1A} agonists or antagonists, especially 5-HT_{1A} partial agonists, neurokinin-1 receptor antagonists, corticotropin releasing factor (CRF) antagonists, and pharmaceutically acceptable salts thereof.

Further, it is understood that compounds of this invention can be administered at prophylactically effective dosage levels to prevent the above-recited conditions and disorders, as well as to prevent other conditions and disorders associated with sodium channel activity.

Creams, ointments, jellies, solutions, or suspensions containing the instant compounds can be employed for topical use. Mouth washes and gargles are included within the scope of topical use for the purposes of this invention.

Dosage levels from about 0.01mg/kg to about 140mg/kg of body weight per day are useful in the treatment of inflammatory and neuropathic pain, or alternatively about 0.5mg to about 7g per patient per day. For example, inflammatory pain may be effectively treated by the

administration of from about 0.01mg to about 75mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day. Neuropathic pain may be effectively treated by the administration of from about 0.01mg to about 125mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 5.5g per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration to humans may conveniently contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1mg to about 1000mg of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg or 1000mg.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors. Such patient-related factors include the age, body weight, general health, sex, and diet of the patient. Other factors include the time and route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

In practice, the compounds represented by Formula I or II, or pharmaceutically acceptable salts thereof, can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compounds represented by Formula I or II, or pharmaceutically acceptable salts thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and

intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of Formula I or II. The compounds of Formula I or II, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents can be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.1mg to about 500mg of the active ingredient and each cachet or capsule preferably containing from about 0.1mg to about 500mg of the active ingredient. Thus, a tablet, cachet, or capsule conveniently contains 0.1mg, 1mg, 5mg, 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, or 500mg of the active ingredient taken one or two tablets, cachets, or capsules, once, twice, or three times daily.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions

can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage, and thusshould be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, and dusting powder. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound represented by Formula I or II, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid, such as, for example, where the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in moulds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, and preservatives (including anti-oxidants). Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound described by Formula I or II, or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

The compounds and pharmaceutical compositions of this invention have been found to block sodium channels. Accordingly, an aspect of the invention is the treatment in mammals of maladies that are amenable to amelioration through blockage of neuronal sodium

channels, including, for example, acute pain, chronic pain, visceral pain, inflammatory pain, and neuropathic pain by administering an effective amount of a compound of this invention. The term "mammals" includes humans, as well as other animals, such as, for example, dogs, cats, horses, pigs, and cattle. Accordingly, it is understood that the treatment of mammals other than humans refers to the treatment of clinical afflictions in non-human mammals that correlate to the above recited afflictions.

Further, as described above, the instant compounds can be utilized in combination with one or more therapeutically active compounds. In particular, the inventive compounds can be advantageously used in combination with i) opiate agonists or antagonists, ii) calcium channel antagonists, iii) 5HT receptor agonists or antagonists iv) sodium channel antagonists, v) N-methyl-D-aspartate (NMDA) receptor agonists or antagonists, vi) COX-2 selective inhibitors, vii) neurokinin receptor 1 (NK1) antagonists, viii) non-steroidal anti-inflammatory drugs (NSAID), ix) selective serotonin reuptake inhibitors (SSRI) and/or selective serotonin and norepinephrine reuptake inhibitors (SSNRI), x) tricyclic antidepressant drugs, xi) norepinephrine modulators, xii) lithium, xiii) valproate, and xiv) neurontin (gabapentin).

The abbreviations used herein have the following tabulated meanings. Abbreviations not tabulated below have their meanings as commonly used unless specifically stated otherwise.

Ac	Acetyl
AIBN	2,2'-azobis(isobutyronitrile)
BINAP	1,1'-bi-2-naphthol
Bn	Benzyl
CAMP	cyclic adenosine-3',5'-monophosphate
DAST	(diethylamino)sulfur trifluoride
DEAD	diethyl azodicarboxylate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	N,N-dimethylformamide
Dppf	1,1'-bis(diphenylphosphino)-ferrocene
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et_3N	Triethylamine

GST	glutathione transferase
HMDS	Hexamethyldisilazide
LDA	lithium diisopropylamide
m-CPBA	metachloroperbenzoic acid
MMPP	monoperoxyphthalic acid
MPPM	monoperoxyphthalic acid, magnesium salt $6H_2O$
Ms	methanesulfonyl = mesyl = SO_2Me
Ms0	methanesulfonate = mesylate
NBS	N-bromo succinimide
NSAID	non-steroidal anti-inflammatory drug
o-Tol	ortho-tolyl
OXONE®	$2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$
PCC	pyridinium chlorochromate
$Pd_2(dba)_3$	Bis(dibenzylideneacetone) palladium(0)
PDC	pyridinium dichromate
PDE	Phosphodiesterase
Ph	Phenyl
Phe	Benzenediyl
PMB	para-methoxybenzyl
Pye	Pyridinediyl
r.t. or RT	room temperature
Rac.	Racemic
SAM	aminosulfonyl or sulfonamide or SO_2NH_2
SEM	2-(trimethylsilyl)ethoxymethoxy
SPA	scintillation proximity assay
TBAF	tetra-n-butylammonium fluoride
Th	2- or 3-thienyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	Tetrahydrofuran
Thi	Thiophenediyl
TLC	thin layer chromatography
TMS-CN	trimethylsilyl cyanide

TMSI	trimethylsilyl iodide
Tz	1H (or 2H)-tetrazol-5-yl
XANTPHOS	4,5-Bis-diphenylphosphanyl-9,9-dimethyl-9H-xanthene
C_3H_5	Allyl

ALKYL GROUP ABBREVIATIONS

Me	=	Methyl
Et	=	ethyl
n-Pr	=	normal propyl
i-Pr	=	isopropyl
n-Bu	=	normal butyl
i-Bu	=	isobutyl
s-Bu	=	secondary butyl
t-Bu	=	tertiary butyl
c-Pr	=	cyclopropyl
c-Bu	=	cyclobutyl
c-Pen	=	cyclopentyl
c-Hex	=	cyclohexyl

The following *in vitro* and *in vivo* assays were used in assessing the biological activity of the instant compounds.

Compound Evaluation (*in vitro* assay):

The identification of inhibitors of the sodium channel is based on the ability of sodium channels to cause cell depolarization when sodium ions permeate through agonist-modified channels. In the absence of inhibitors, exposure of an agonist-modified channel to sodium ions will cause cell depolarization. Sodium channel inhibitors will prevent cell depolarization caused by sodium ion movement through agonist-modified sodium channels. Changes in membrane potential can be determined with voltage-sensitive fluorescence resonance energy transfer (FRET) dye pairs that use two components, a donor coumarin (CC_2DMPE) and an acceptor oxanol ($DiSBAC_2(3)$). Oxanol is a lipophilic anion and distributes across the

membrane according to membrane potential. In the presence of a sodium channel agonist, but in the absence of sodium, the inside of the cell is negative with respect to the outside, oxanol is accumulated at the outer leaflet of the membrane and excitation of coumarin will cause FRET to occur. Addition of sodium will cause membrane depolarization leading to redistribution of oxanol to the inside of the cell, and, as a consequence, to a decrease in FRET. Thus, the ratio change (donor/acceptor) increases after membrane depolarization. In the presence of a sodium channel inhibitor, cell depolarization will not occur, and therefore the distribution of oxanol and FRET will remain unchanged.

Cells stably transfected with the PN1 sodium channel (HEK-PN1) were grown in polylysine-coated 96-well plates at a density of ca. 140,000 cells/well. The media was aspirated, and the cells were washed with PBS buffer, and incubated with 100μL of 10μM CC_2-DMPE in 0.02% pluronic acid. After incubation at 25°C for 45min, media was removed and cells were washed 2x with buffer. Cells were incubated with 100μL of $DiSBAC_2(3)$ in TMA buffer containing 20μM veratridine, 20nM brevetoxin-3, and test sample. After incubation at 25°C for 45min in the dark, plates were placed in the VIPR instrument, and the fluorescence emission of both CC_2-DMPE and $DiSBAC_2(3)$ recorded for 10s. At this point, 100μL of saline buffer was added to the wells to determine the extent of sodium-dependent cell depolarization, and the fluorescence emission of both dyes recorded for an additional 20s. The ratio CC_2-DMPE/$DiSBAC_2(3)$, before addition of saline buffer equals 1. In the absence of inhibitors, the ratio after addition of saline buffer is > 1.5. When the sodium channel has been completely inhibited by either a known standard or test compound, this ratio remains at 1. It is possible, therefore, to titrate the activity of a sodium channel inhibitor by monitoring the concentration-dependent change in fluorescence ratio.

Electrophysiological Assays (*In Vitro* assays):

Cell preparation: A HEK-293 cell line stably expressing the PN1 sodium channel subtype was established in-house. The cells were cultured in MEM growth media (Gibco) with 0.5mg/mL G418, 50 units/mL Pen/Strep and 1mL heat-inactivated fetal bovine serum at 37°C and 10% CO_2. For electrophysiological recordings, cells were plated on 35mm dishes coated with poly-D-lysine.

Whole-cell recordings: HEK-293 cells stably expressing the PN1 sodium channel subtype were examined by whole cell voltage clamp (Hamill et. al. Pfluegers Archives 391:85-100 (1981)) using an EPC-9 amplifier and Pulse software (HEKA Electronics, Lamprecht, Germany). Experiments were performed at room temperature. Electrodes were fire-polished to

resistances of 2-4 MΩ. Voltage errors were minimized by series resistance compensation, and the capacitance artifact was canceled using the EPC-9's built-in circuitry. Data were acquired at 50 kHz and filtered at 7-10 kHz. The bath solution consisted of 40 mM NaCl, 120 mM NMDG Cl, 1 mM KCl, 2.7 mM $CaCl_2$, 0.5 mM $MgCl_2$, 10 mM NMDG HEPES, pH 7.4, and the internal (pipet) solution contained 110 mM Cs-methanesulfonate, 5 mM NaCl, 20mM CsCl, 10mM CsF, 10 mM BAPTA (tetra Cs salt), 10 mM Cs HEPES, pH 7.4.

The following protocols were used to estimate the steady-state affinity of compounds for the resting and inactivated state of the channel (K_r and K_i, respectively):

1) 8ms test-pulses to depolarizing voltages from –60mV to +50mV from a holding potential of –90mV were used to construct current-voltage relationships (IV-curves). A voltage near the peak of the IV-curve (typically –10 or 0 mV) was used as the test-pulse voltage throughout the remainder of the experiment.

2) Steady-state inactivation (availability) curves were constructed by measuring the current activated during an 8ms test-pulse following 10s conditioning pulses to potentials ranging from –120mV to –10mV.

3) Compounds were applied at a holding potential at which 20-50% of the channels was inactivated and sodium channel blockage was monitored during 8ms test pulses at 2s intervals.

4) After the compounds equilibrated, the voltage-dependence of steady-state inactivation in the presence of compound was determined according to protocol 2) above. Compounds that block the resting state of the channel decrease the current elicited during test-pulses from all holding potentials, whereas compounds that primarily block the inactivated state shift the mid-point of the steady-state inactivation curve. The maximum current at negative holding potentials (I_{max}) and the difference in the mid-points of the steady-state inactivation curves (□V) in control and in the presence of a compound were used to calculate K_r and K_i using the following equations:

$$K_r = \frac{[Drug] * I_{Max,Drug}}{I_{Max,Control} - I_{Max,Drug}}$$

$$K_i = \frac{[Drug]}{\left(1 + \frac{[Drug]}{K_r}\right) * e^{\frac{-\Delta V}{k}} - 1}$$

In cases where the compound did not affect the resting state, K_i was calculated using the following equation:

$$K_i = \frac{[Drug]}{e^{\frac{-\Delta V}{k}} - 1}$$

Rat Formalin Paw test (*in vivo* assay):

Compounds were assessed for their ability to inhibit the behavioral response evoked by a 50μL injection of formalin (5%). A metal band was affixed to the left hind paw of male Sprague-Dawley rats (Charles River, 200-250g) and each rat was conditioned to the band for 60min within a plastic cylinder (15cm diameter). Rats were dosed with either vehicle or a test compound either before (local) or after (systemic) formalin challenge. For local administration, compounds were prepared in a 1:4:5 vehicle of ethanol, PEG400 and saline (EPEGS) and injected subcutaneously into the dorsal surface of the left hind paw 5min prior to formalin. For systemic administration, compounds were prepared in either a EPEGS vehicle or a Tween80 (10%)/sterile water (90%) vehicle and were injected i.v. (via the lateral tail vein 15min after formalin) or p.o. (60min before formalin). The number of flinches was counted continuously for 60min using an automated nociception analyzer (UCSD Anesthesiology Research, San Diego, CA). Statistical significance was determined by comparing the total flinches detected in the early (0-10min) and late (11-60min) phase with an unpaired t-test.

***In vivo* assay using Rat CFA model:**

Unilateral inflammation was induced with a 0.2 ml injection of complete Freund's adjuvant (CFA: Mycobacterium tuberculosis, Sigma; suspended in an oil/saline (1:1) emulsion; 0.5mg Mycobacterium/mL) in the plantar surface of the left hindpaw. This dose of CFA produced significant hind paw swelling but the animals exhibited normal grooming behavior and weight gain over the course of the experiment. Mechanical hyperalgesia was assessed 3 days after tissue injury using a Randall-Selitto test. Repeated Measures ANOVA, followed by Dunnett's Post Hoc test.

SNL: Mechanical Allodynia (*in vivo* assay):

Tactile allodynia was assessed with calibrated von Frey filaments using an up-down paradigm before and two weeks following nerve injury. Animals were placed in plastic cages with a wire mesh floor and allowed to acclimate for 15min before each test session. To

determine the 50% response threshold, the von Frey filaments (over a range of intensities from 0.4 to 28.8g) were applied to the mid-plantar surface for 8s, or until a withdrawal response occurred. Following a positive response, an incrementally weaker stimulus was tested. If there was no response to a stimulus, then an incrementally stronger stimulus was presented. After the initial threshold crossing, this procedure was repeated for four stimulus presentations per animal per test session. Mechanical sensitivity was assessed 1 and 2 hr post oral administration of the test compound.

The compounds described in this invention displayed sodium channel blocking activity of from about <0.1μM to about <50μM in the *in vitro* assays described above. It is advantageous that the compounds display sodium channel blocking activity of <5μM in the *in vitro* assays. It is more advantageous that the compounds display sodium channel blocking activity of <1μM in the *in vitro* assays. It is even more advantageous that the compounds display sodium channel blocking activity of <0.5μM in the *in vitro* assays. It is still more advantageous that the compounds display sodium channel blocking activity of <0.1μM in the *in vitro* assays.

The present compounds can be prepared according to the general schemes provided below as well as the procedures provided in the Examples. The following Schemes and Examples further describe, but do not limit, the scope of the invention.

Unless specifically stated otherwise, the experimental procedures were performed under the following conditions: All operations were carried out at room or ambient temperature; that is, at a temperature in the range of 18-25°C. Evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000pascals: 4.5-30mm. Hg) with a bath temperature of up to 60°C. The course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only. Melting points are uncorrected and 'd' indicates decomposition. The melting points given are those obtained for the materials prepared as described. Polymorphism may result in isolation of materials with different melting points in some preparations. The structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data. When given, yields are for illustration only. When given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300MHz, 400MHz or 500MHz using the indicated solvent. Conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc. In addition, "Ar" signifies an aromatic signal. Chemical symbols have their usual meanings; the following abbreviations

are used: v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

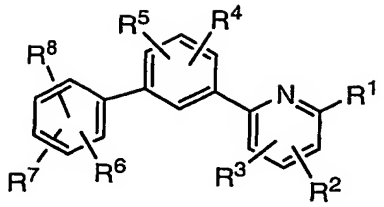
Methods of Synthesis

Compounds of the present invention can be prepared according to the following methods. The substituents are the same as in the above Formulas except where defined otherwise.

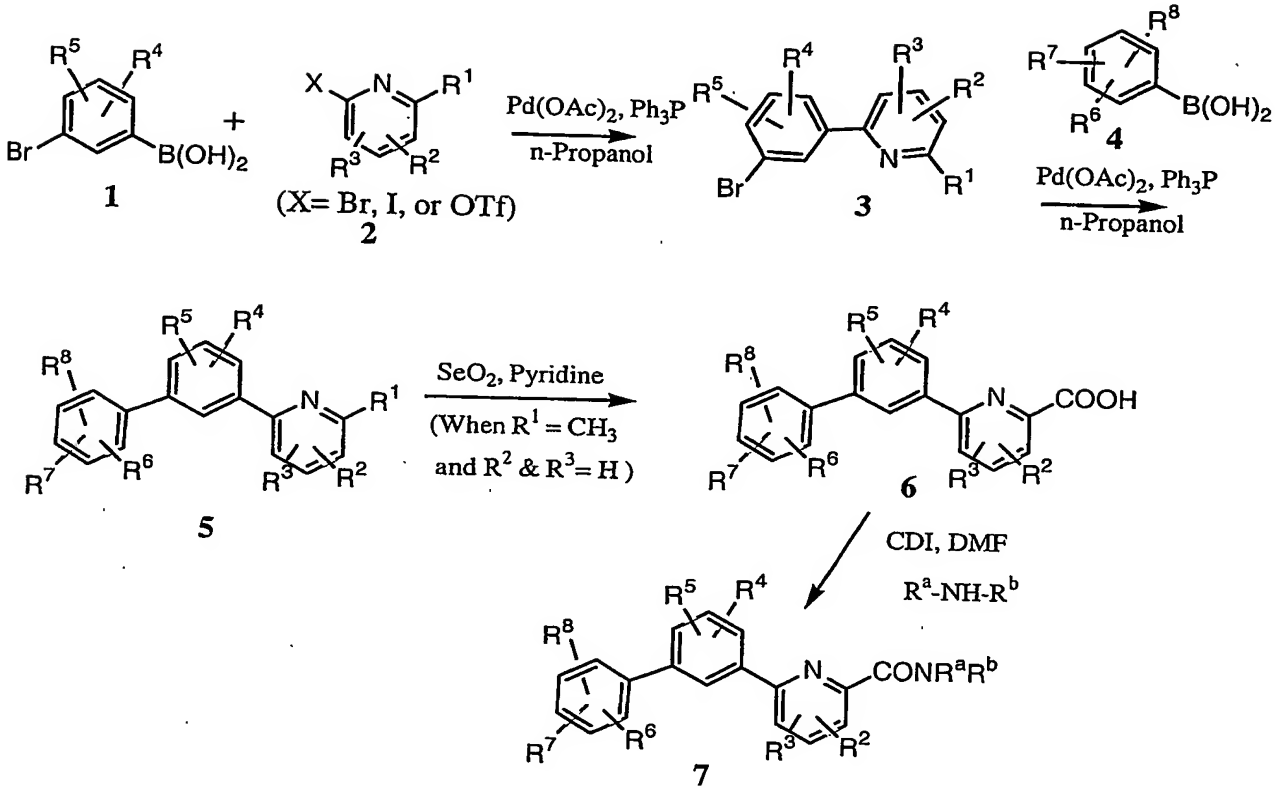
The novel compounds of the present invention can be readily synthesized using techniques known to those skilled in the art, such as those described, for example, in Advanced Organic Chemistry, March, 4th Ed., John Wiley and Sons, New York, NY, 1992 ; Advanced Organic Chemistry, Carey and Sundberg, Vol. A and B, 3rd Ed., Plenum Press, Inc., New York, NY, 1990; Protective groups in Organic Synthesis, Green and Wuts, 2nd Ed., John Wiley and Sons, New York, NY, 1991; Comprehensive Organic Transformations, Larock, VCH Publishers, Inc., New York, NY, 1988; Handbook of Heterocyclic Chemistry, Katritzky and Pozharskii, 2nd Ed., Pergamon, New York, NY, 2000 and references cited therein. The starting materials for the present compounds may be prepared using standard synthetic transformations of chemical precursors that are readily available from commercial sources such as Aldrich Chemical Co. (Milwaukee, WI); Sigma Chemical Co. (St. Louis, MO); Lancaster Synthesis (Windham, N.H.); Ryan Scientific (Columbia, S. C.); Maybridge (Cornwall, UK); Matrix Scientific (Columbia, S. C.); Arcos, (Pittsburgh, PA) and Trans World Chemicals (Rockville, MD).

The procedures described herein for synthesizing the compounds may include one or more steps of protecting group manipulations and various purification steps, such as, recrystallization, distillation, column chromatography, flash chromatography, thin-layer chromatography (TLC), radial chromatography and high-pressure chromatography (HPLC). The products can be characterized using various techniques well known in chemical arts, such as, proton and carbon-13 nuclear magnetic resonance (^{1}H and ^{13}C NMR), infrared and ultraviolet spectroscopy (IR and UV), X-ray crystallography, elemental analysis and HPLC and mass spectrometry (LC-MS). Methods of protecting group manipulation, purification, structure identification and quantification are well known to one skilled in the art of chemical synthesis.

Pyridine compounds of the present invention as represented by the formula shown immediately below can be prepared as outlined in SCHEME 1.



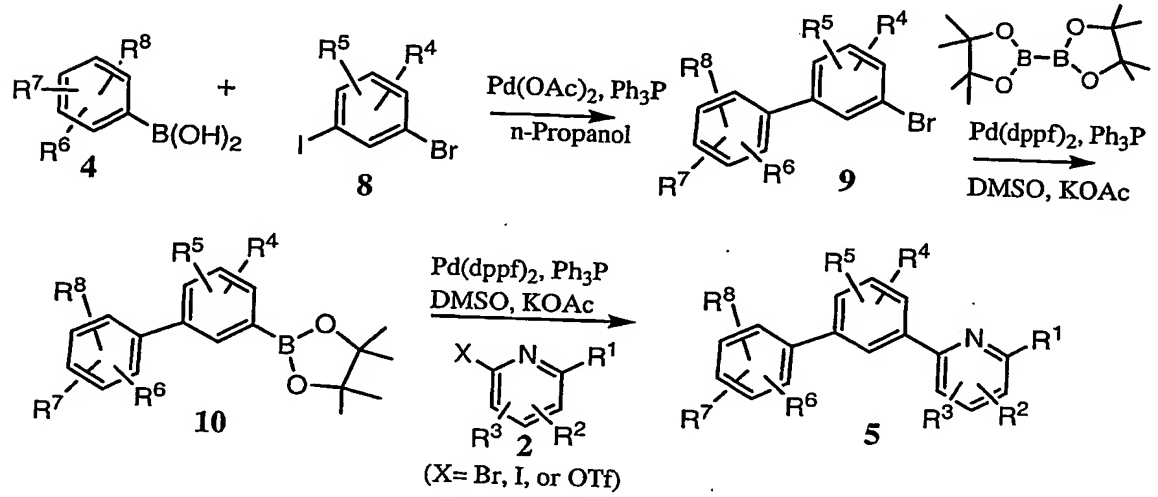
SCHEME 1



An appropriate bromo, iodo pyridine or trifluoromethanesulfonate (triflate) derivative **2** can be subjected to the Pd-catalyzed cross-coupling reaction (Suzuki reaction) [Huff, B. et al., *Org. Synth.* 75: 53-60 (1997); Goodson, F. E. et al. *Org. Synth.* 75: 61-68 (1997)] in the presence of an appropriately substituted aryl boronic acid **1** to provide **3,** which can be then subjected to a second cycle of Suzuki reaction with **4** to give the biaryl pyridine compound **5**. When R^5 in **5** is a methyl group (R_5 = Me), it can be oxidized under a mild condition as described to provide the carboxylic acid **6**. The acid **6** can be converted to the amide **7** using an approprite amine R^9-NH-R^{10} in the presence of an approprite carboxylic acid activating agent,

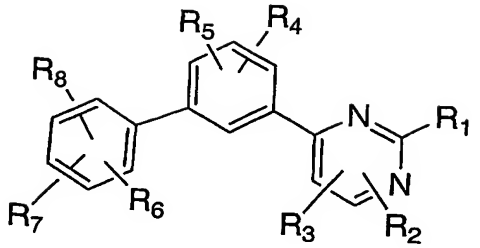
such as carbonyl-di- imidazole (CDI). Alternatively, an appropriate ester or amide derivative of the commercially available 6-bromo-picolinic acid can be used in the synthesis of **7**. The regioisomers of **7** also can be prepared by employing a similar sequence of reactions using appropriately substituted pyridine derivatives.

SCHEME 2

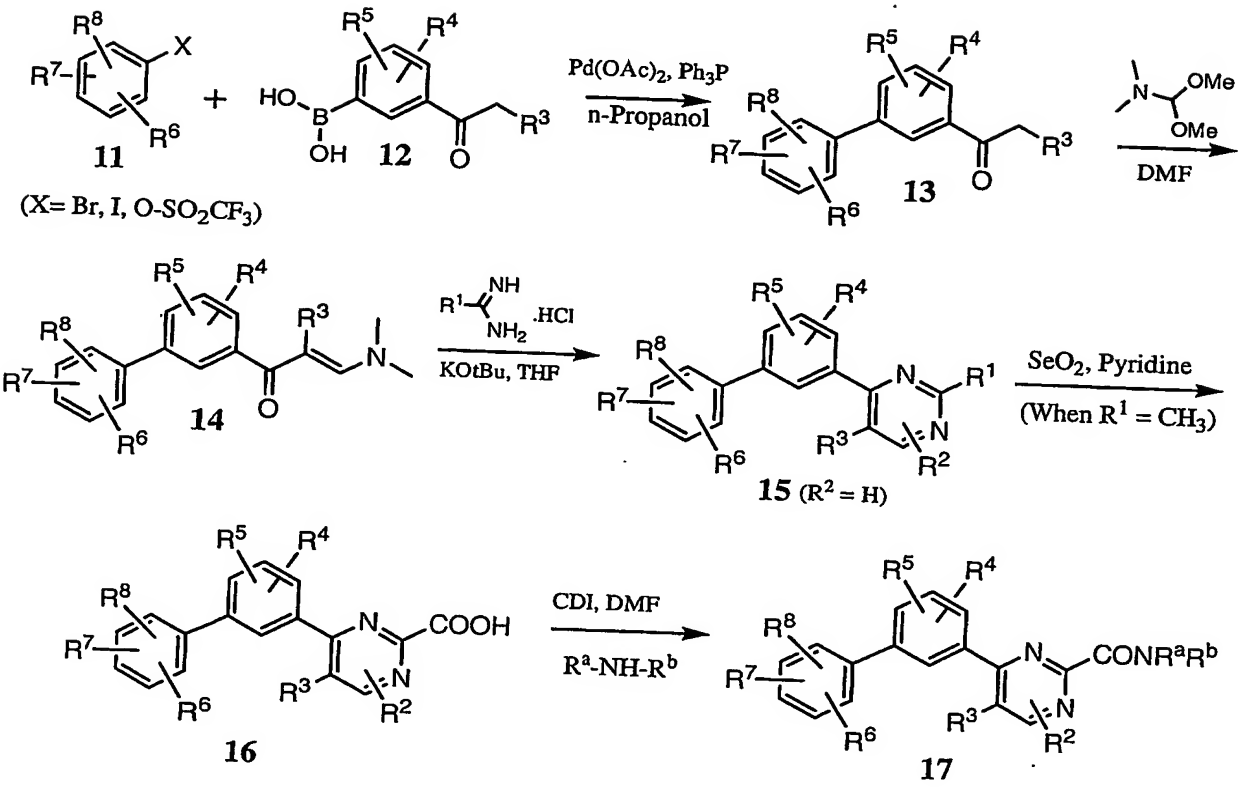


In an alternative approach to preparing pyridine compounds of the instant invention, the boronic acid **4** can be coupled with an appropriately substituted bromo, iodo or triflate derivative of **8** to provide the biphenyl **9**, which can then be converted into the corresponding boronic acid ester **10** under the conditions described. The appropriate aryl or heteroaryl compound **2** can be then be coupled under Pd-catalyzed cross-coupling reaction condition to provide **5**.

Compounds of the instant invention represented by the formula shown immediately below can be prepared as outlined in SCHEME 3.



SCHEME 3

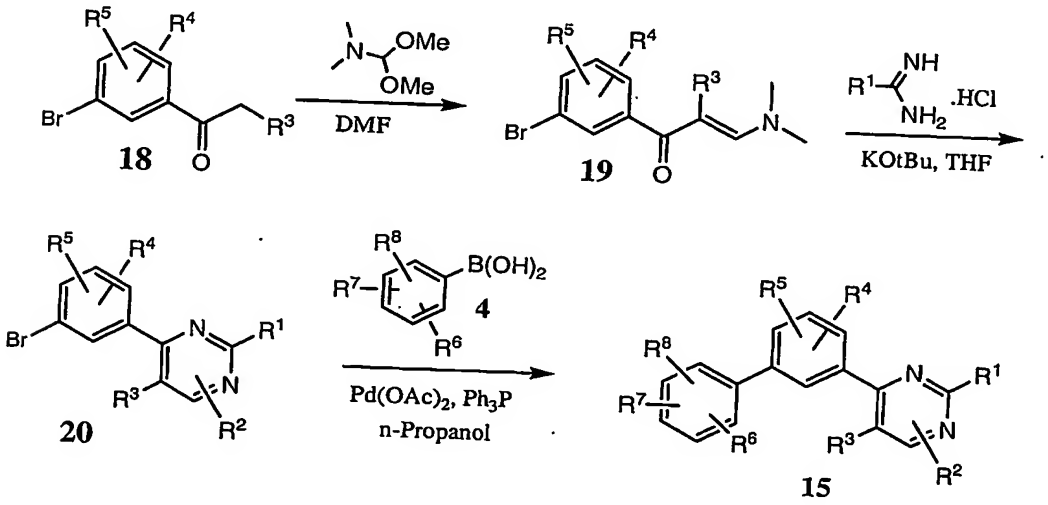


An appropriate aryl halide or aryl triflate **11** can be reacted with an appropriate boronic acid **12** under Pd-catalyzed cross-coupling reaction (Suzuki reaction) conditions to provide the ketone **13**. The ketone can be converted to the intermediate **14**, which can be then converted to the desired pyrimidine derivative **15** using the methods described by Domagala, J. M. et al. [*J. Heterocyclic Chem.* 26: 1147-1158 (1989)] and Fischer, G. W. [*J. Heterocyclic Chem.* 26: 1147-1158 (1989)]. The methyl pyrimidine **15** (when $R^1 = CH_3$) can be oxidized with SeO_2 using the conditions described by Sakamoto, T. *et al.* [*Chem Pharm. Bull.* 28: 571-

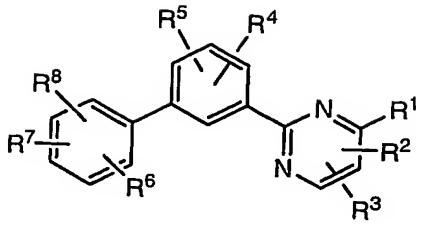
577(1980)] to provide the corresponding carboxylic acid **16**, which could then be elaborated into appropriate analogs including the amide **17** as described.

Alternatively, the biaryl pyrimidine **15** can also be synthesized by Pd-catalyzed cross-coupling reaction between the pyrimidine **20** and an appropriate aryl boronic acid **21** as outlined in **SCHEME 4**. A variety of aryl boronic acids are commercially available or these can be prepared conveniently from the corresponding aryl bromide or iodide by converting it to an organolithium derivative [Baldwin, J. E. et al. *Tetrahedron Lett.* 39: 707-710 (1998)] or a Grignard reagent followed by treatment with trialkylborate [Li, J. J. et al, *J. Med. Chem*, 38: 4570-4578(1995) and Piettre, S. R. et al. *J. Med Chem.* 40: 4208-4221 (1997)]. Aryl boronates can also be used as an alternative to aryl boronic acids in these Pd-catalyzed coupling reactions [Giroux, A. et. al., *Tetrahedron Lett.*, 38: 3841(1997)]. The boronates can be easily prepared from the aryl bromides, iodides and trifluoromethane sulfonates using the method described by Murata, M. et. al. [*J. Org. Chem.* 65: 164-168 (2000)].

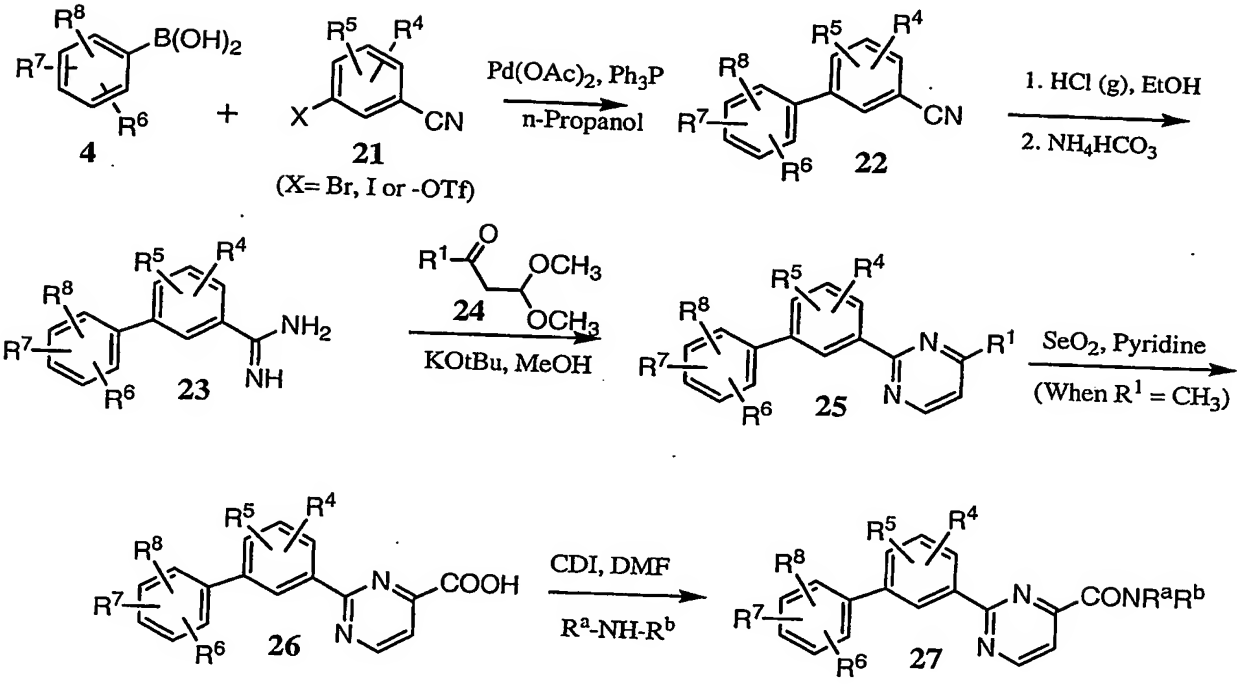
SCHEME 4



Compounds of the instant invention represented by the formula shown immediately below can be prepared from the biphenyl nitrile 22 as illustrated in

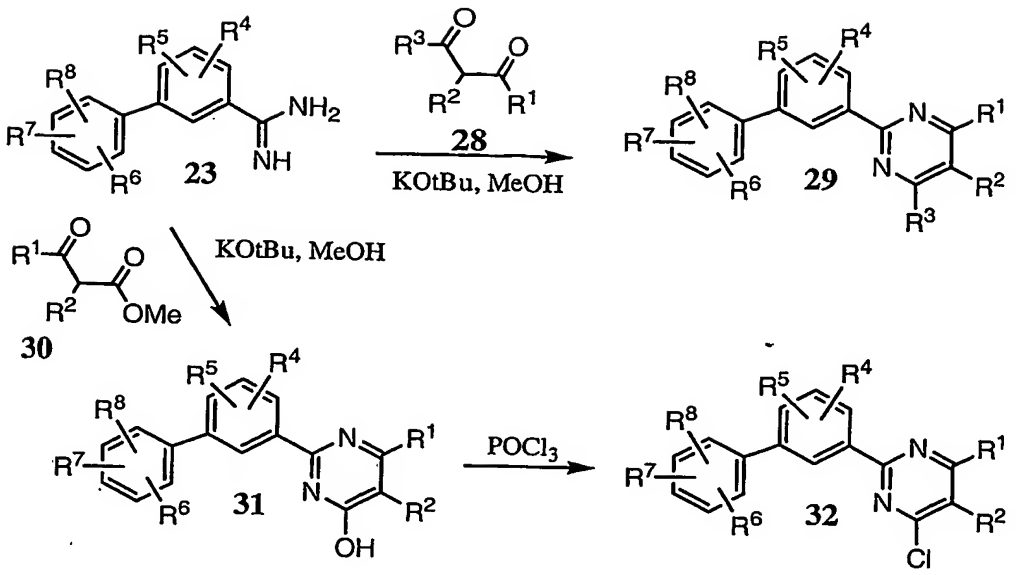


SCHEME 5



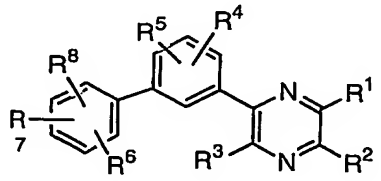
The nitrile **22** can be prepared from the Pd-catalyzed coupling of the boronic acid **4** with an appropriately substituted benzonitrile **21**. The nitrile **22** can then be converted into the amidine **23** as oulined. The reaction of **23** with with an appropriate β-keto aldehyde derivative (**24**) can provide the desired pyrimidine **25**. The R^1 substituent can be then manipulated to provide the carboxylic acid **26** and the corrsponding amides **27**, as outlined.

SCHEME 6

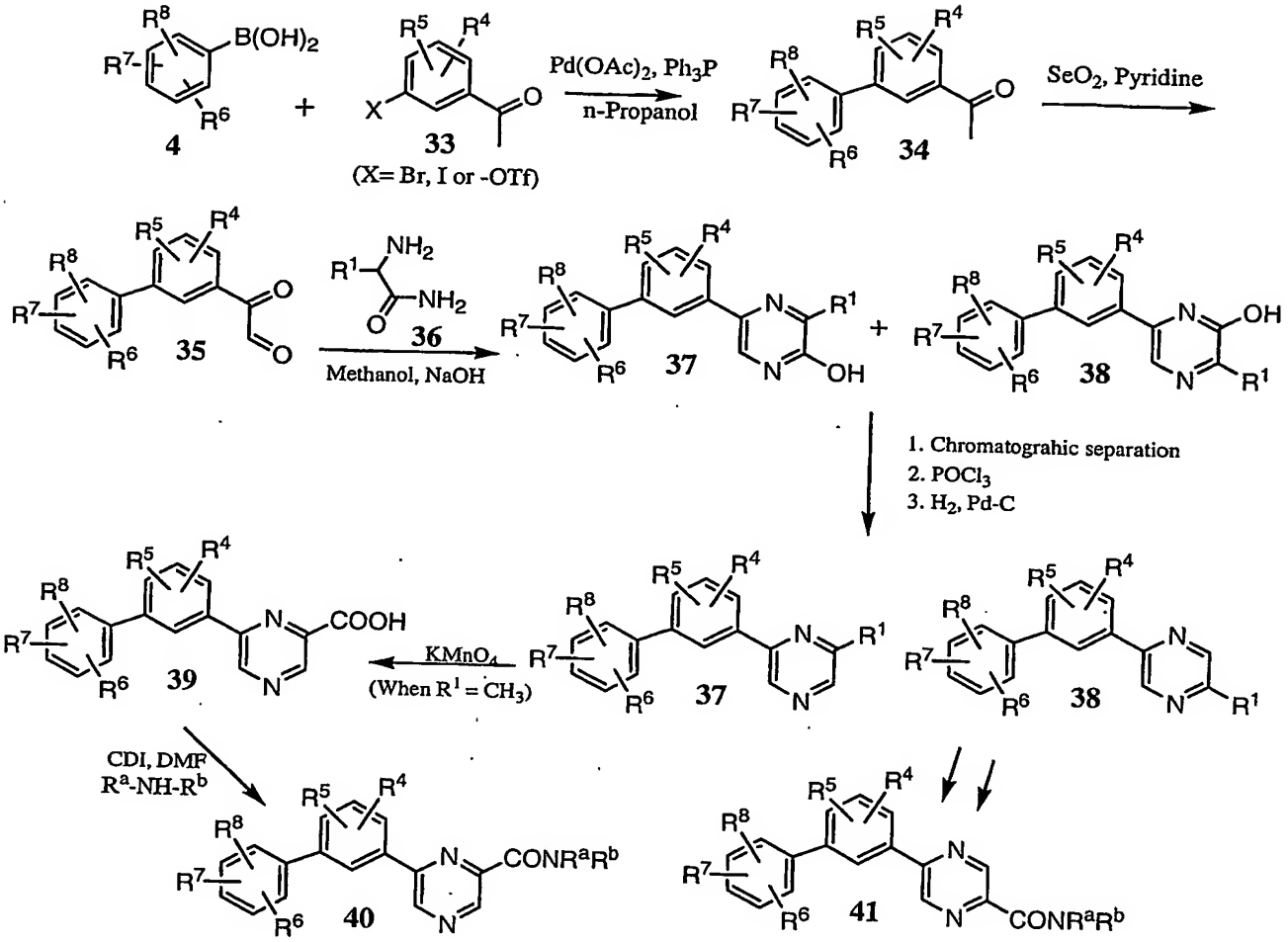


Alternatively, according to **SCHEME 6**, a reaction of β-diketones such as **28** with the amidine **23** may also provide a 4,6-disubstituted pyrimidine **29** (where R^2 =H). Similarly, the pyrimidone **31** can be synthesized by reacting an appropriate β-ketoester **30** with **23** (SCHEME **6**). The pyrimidone **31** can be easily transformed into the corresponding chloro derivative **32**. Replacement of the chloro group in **32** with appropriate nucleophillic reagents may provide a series analogs of **32** that can be further elaborated.

Pyrazine compounds of the present invention represented by the formula shown immediately below can be prepared as shown in **SCHEME 7**.

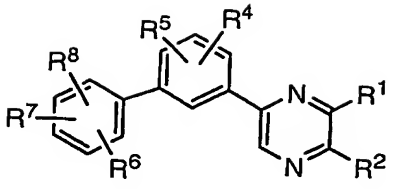


SCHEME 7

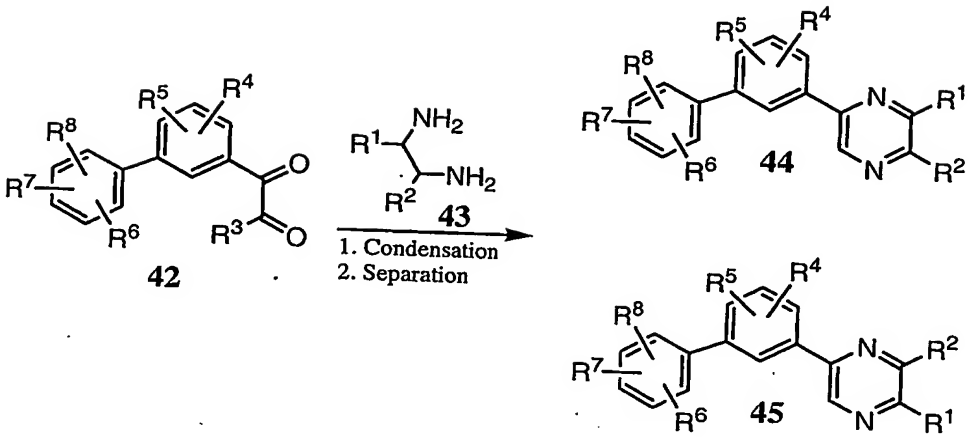


The dicarbonyl compound **35**, obtained from **34**, can be reacted in an appropriate solvent with an appropriate α-aminocarboxamide **36** to provide a regioisomeric mixture of pyrazinones **37** and **38**, which can be separated and transformed into appropriate pyrazine derivatives such as **39**, **40** and **41**.

Pyrazine compounds of the instant invention represented by the formula shown immediately below can also be prepared as outlined in **SCHEME 8**.



SCHEME 8



Appropriate solvents are those which will at least partially dissolve one or all of the reactants and will not adversely interact with either the reactants or the product. Suitable solvents are aromatic hydrocarbons (e.g, toluene, xylenes), halogenated solvents (e.g, methylene chloride, chloroform, carbontetrachloride, chlorobenzenes), ethers (e.g, diethyl ether, diisopropylether, tert-butyl methyl ether, diglyme, tetrahydrofuran, dioxane, anisole), nitriles (e.g, acetonitrile, propionitrile), ketones (e.g, 2-butanone, dithyl ketone, tert-butyl methyl ketone), alcohols (e.g, methanol, ethanol, n-propanol, iso-propanol, n-butanol, t-butanol), dimethyl formamide (DMF), dimethylsulfoxide (DMSO) and water. Mixtures of two or more solvents can also be used. Suitable bases are, generally, alkali metal hydroxides, alkaline earth metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide, barium hydroxide, and calcium hydroxide; alkali metal hydrides and alkaline earth metal hydrides such as lithium hydride, sodium hydride, potassium hydride and calcium hydride; alkali metal amides such as lithium amide, sodium amide and potassium amide; alkali metal carbonates and alkaline earth metal carbonates such as lithium carbonate, sodium carbonate, Cesium carbonate, sodium hydrogen carbonate, and cesium hydrogen carbonate; alkali metal alkoxides and alkaline earth

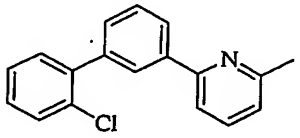
metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and magnesium ethoxide; alkali metal alkyls such as methyllithium, n-butyllithium, sec-butyllithium, t-bultyllithium, phenyllithium, alkyl magnaesium halides, organic bases such as trimethylamine, triethylamine, triisopropylamine, N,N-diisopropylethylamine, piperidine, N-methyl piperidine, morpholine, N-methyl morpholine, pyridine, collidines, lutidines, and 4-dimethylaminopyridine; and bicyclic amines such as DBU and DABCO.

As described previously, in preparing the compositions for oral dosage form, any of the usual pharmaceutical media can be employed. For example, in the case of oral liquid preparations such as suspensions, elixirs and solutions, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used; or in the case of oral solid preparations such as powders, capsules and tablets, carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be included. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. In addition to the common dosage forms set out above, controlled release means and/or delivery devices may also be used in administering the instant compounds and compositions.

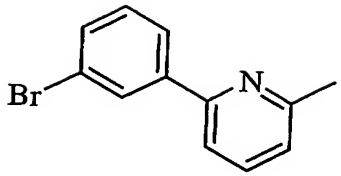
It is understood that the functional groups present in compounds described in the above schemes can be further manipulated, when appropriate, using the standard functional group transformation techniques available to those skilled in the art, to provide desired compounds described in this invention.

Other variations or modifications, which will be obvious to those skilled in the art, are within the scope and teachings of this invention. This invention is not to be limited except as set forth in the following claims.

EXAMPLE 1



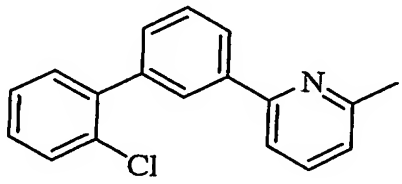
Step 1: Preparation of:



A 100-ml round-bottom flask fitted with a stirbar, condenser, and septum was flushed with N_2 and charged with 2-bromo-6-methyl pyridine (1.50g), toluene (36 mL), deionized water (18 mL), and ethanol (18 mL). 3-bromophenylboronic acid (1.84g) was then added to the mixture followed by sodium carbonate (1.85 g). Finally, tetrakis(triphenylphosphine) palladium (0) (0.508g) was added to the solution quickly, and the reaction was refluxed. After two hours, the reaction was cooled to room temperature and partitioned between EtOAc and water. The aqueous layer was extracted a second time with EtOAc. The combined organic phase was dried over sodium sulfate and concentrated in vacuo. The crude material obtained was purified by column chromatography on silica gel using a gradient of 5-8% EtOAc in hexanes to yield the pure desired bromo compound.

MS: m/e 249/251 $(M+1)^+$

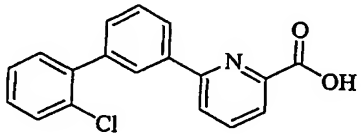
Step 2: Preparation of



A 25-ml round-bottom flask fitted with a stirbar, condenser, and septum was flushed with N_2 and charged with the bromo compound from step1 above (0.455g), toluene (6 mL), deionized water (3mL), and ethanol (3 mL). 2-chlorophenylboronic acid (572mg) was then added followed by sodium carbonate (0.388g). To the resulting solution, tetrakis(triphenylphosphine) palladium (0) (0.106g) was added quickly. The reaction was refluxed for two hours and then cooled to room temperature. The mixture was partitioned between EtOAc and water. The aqueous layer was extracted a second time with EtOAc. The combined organic phase was dried over sodium sulfate and concentrated in vacuo. The crude

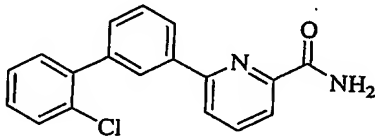
material, thus obtained, was purified by column chromatography on silica gel using 8% EtOAc in hexanes to provide the desired biphenyl pyridineMS: m/e 280 $(M+1)^+$

EXAMPLE 2



To a solution of the methyl pyridyl compound (0.475g) from Step 2 of Example 1 and anhydrous pyridine (7 mL) was added selenium dioxide (1.30g). The mixture was refluxed overnight (~18 hours). An additional 8 equivalents of selenium dioxide were added and the reaction was allowed to proceed for another 30 hours. The reaction was cooled to room temperature and filtered through a pad of Celite. The filtrate was concentrated *in vacuo*. The crude material was purified by reverse-phase column chromatography using CH3CN-water containing 0.1% TFA to provide the desired carboxylic acid.MS: m/e 310 $(M+1)^+$

EXAMPLE 3



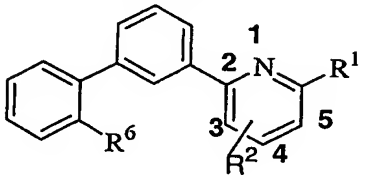
The carboxylic acid from Example 2 (0.09g) was dissolved in anhydrous DMF (6mL) in a 10-ml round bottom flask under N_2. Carbonyl-di-imidazole (CDI) (0.094g) was added and the solution was stirred at room temperature for 1 hour. Solid ammonium acetate (0.089g) was then added and stirring continued overnight at room temperature. The reaction was quenched with water (~ 4mL) and extracted with 2 x 4ml portions of EtOAc. The organic phase was dried over sodium sulfate and concentrated *in vacuo*. The crude material was then purified by column chromatography on silica gel using 50% EtOAc in hexanes to give the pure desired amide.

^{1}H NMR ($CDCl_3$): 5.89(s, 1H), 7.36-7.42 (m, 2H), 7.47 (d, J=7.3 Hz, 1H), 7.56-7.64 (m, 3H), 7.97-8.01 (m, 2H), 8.05 (s, 1H), 8.07 (d, J=7.8 Hz, 1H), 8.15 (s, 1H), 8.23 (d, J=6.2 Hz, 1H)

MS (ESI): m/e 309 $(M+1)^+$

Other Examples of the instant compounds are given below in **TABLE 1.**

TABLE 1

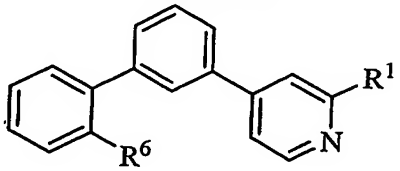


EXAMPLE #	R^6	R^2	R^1	MS (m/e, M+1)
4	OCF_3	5-CO_2CH_3	H	374
5	OCF_3	5-CH_3	H	330
6	OCF_3	5-COOH	H	360
7	OCF_3	4-CH_3	H	330
8	OCF_3	4-COOH	H	360
9	OCF_3	4-$CONH_2$	H	359
10	OCF_3	3-CO_2CH_3	H	374
11	OCF_3	3-CH_3	H	330
12	OCF_3	3-COOH	H	360
13	OCF_3	3-$CONH_2$	H	359
14	OCF_3	H	CH_3	330
15	OCF_3	H	COOH	360
16	OCF_3	4-CH_3	$CONH_2$	359
17	CF_3	4-COOH	H	314
18	CF_3	3-CH_3	H	344
19	CF_3	H	H	314
20	CF_3	H	CH_3	314
21	CF_3	H	COOH	344
22	CF_3	H	$CONH_2$	343
23	Cl	4-CH_3	H	280

EXAMPLE #	R^6	R^2	R^1	MS (m/e, M+1)
24	Cl	4-COOH	H	310
25	Cl	3-CH_3	H	280
26	OCF_3	3-OCH_3	H	280

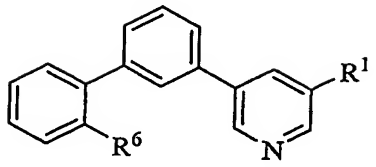
Further Examples of this invention are shown in **TABLE 2** and **TABLE 3.**

TABLE 2



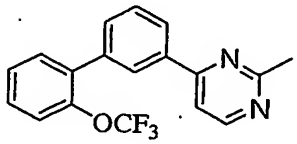
EXAMPLE #	R^6	R^1	MS (m/e, M+1)
27	OCF_3	Me	330
28	OCF_3	COOH	360
29	OCF_3	$CONH_2$	359
30	CF_3	Me	314
31	CF_3	COOH	344
32	CF_3	$CONH_2$	343

TABLE 3



EXAMPLE #	R^6	R^1	MS (m/e, M+1)
33	OCF_3	CO_2Me	374
34	OCF_3	COOH	360
35	OCF_3	$CONH_2$	359

EXAMPLE 36

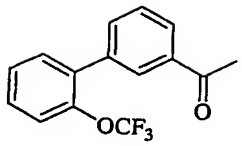


Step 1: 2-(Trifluoromethoxy)phenylboronic acid:

n-Butyllithium (5.9 ml, 9.5 mmol) was added to a solution of 1-bromo-2-(trifluoromethoxy)benzene (2 g, 8.2 mmol) in tetrahydrofuran (28 ml) at –78°C and stirred for 45 minutes. Triisopropyl borate (2.58 ml, 11.1 mmol) was added dropwise to the reaction mixture and the solution was slowly brought to room temperature over 16 hours. The reaction mixture was quenched with water, made basic with 2N NaOH and extracted with ethyl acetate. The aqueous solution was acidified with 2N HCl, stirred for 1 hour at room temperature and extracted into ethyl acetate. The organic layer was washed with water, brine solution and dried over sodium sulfate. It was filtered and concentrated to give the product (1.10 g, 65%) as a white solid.

^{1}HNMR ($CDCl_3$)(δ, ppm): 7.96 (dd, *J*= 7.2, 1.6 Hz, 1 H), 7.53 (ddd, *J* = 9.1, 7.3, 1.8 Hz, 1 H), 7.38 (td, *J* = 7.3, 0.7 Hz, 1 H), 7.28 (d, *J* = 8.2 Hz, 1 H), 5.25 (br s, 2H). MS (M+H): 206.9.

Step 2: Preparation of

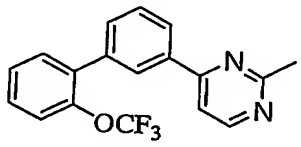


To a solution of 2-bromo(trifluoromethoxy)benzene (4.82g, 20 mmol) (from Step 1) in n-propanol (35 mL) was added 3-acetylbenzeneboronic acid (3.61 g, 22 mmol) under N_2. After 15 min. of stirring at room temperature, Ph_3P (0.46g, 1.7 mmol) was added followed by 2M sodium carbonate (11 mL)and water (10 mL). To the well stirred solution, palladium acetate (50mg) was finally added quickly, and the reaction mixture was refluxed for 4 hours. The reaction was allowed to cool to room temperature and partitioned between EtOAc and water. The aqueous layer was extracted a second time with EtOAc. The combined organic phase was dried over sodium sulfate and concentrated *in vacuo*. The crude material, thus obtained, was purified by column chromatography on silica gel using 5% EtOAc in hexanes to yield the pure ketone as an oil. Yield: 4.45g (79%).

NMR ($CDCl_3$)(δ, ppm): 8.09 (s, 1H), 8.06 (d, 1H), 7.71 (d,2H), 7.58 (t, 1H), 7.50-7.40(m, 4H), 2.67 (s, 3H).

MS(ESI): m/e 281 $(M+1)^+$

Step 3: Preparation of



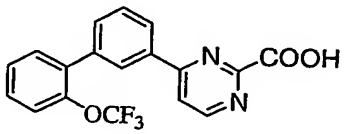
The ketone (1.12g, 4 mmol), from Step 2 above, was dissolved in dry DMF (5 mL) and N, N-dimethyl formamide dimethyl acetal (0.59mL, 4.2 mmol) was added. The resulting mixture was refluxed overnight. The mixture was then cooled and partitioned between EtOAc and water. The organic phase was separated, dried over sodium sulfate and concentrated *in vacuo* to give an orange colored solid (1.35g, 95 %). MS (ESI): m/e 336.1 $(M+1)^+$. A solution of the solid (0.335g, 1 mmol) in anhydrous THF (2 mL) was then added to an aged acetamidine in THF suspension (prepared by refluxing a mixture of acetamidine hydrochloride (0.177g, 1.5 mmol) and potassium t-butoxide (0.168g, 1.5 mmol) in THF (5mL) for 1 hour). The orange

suspension was then refluxed overnight. After cooling to room temperature, the reaction mixture was diluted in water, and extracted with EtOAc (3 times). The combined organic layer was washed with brine, and dried over anhydrous sodium sulfate. After concentration, the crude product was purified by column chromatograghy on silica gel using 33 % EtOAc in hexane to afford desired product as a foam (0.28g) in 81% yield.

^{1}H NMR ($CDCl_3$) (δ, ppm): 8.70 (d, J=5.0 Hz, 1H), 8.18 (m, 1H), 8.11 (q, J=4.5, 7.0 Hz, 1H), 7.50 (m, 3H), 7.45 (t, J=3.0 Hz, 1H), 7.34 (t, J=9.0 Hz, 1H), 7.22 (t, J=9.0 Hz, 1H), 2.82 (s, 1H).

MS(ESI): m/e 331.1 $(M+1)^+$

EXAMPLE 37

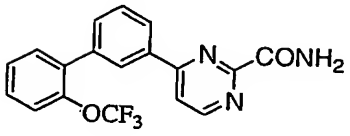


To a solution of the pyrimidine (0.27 g, 0.818 mmol), from Step 3 of Example 36, in dry pyridine (5 mL) was added SeO_2 (0.32g, 2.8 mmol), and the mixture was refluxed overnight. The reaction was cooled to room temperature and filtered through a pad of Celite. The filtrate was concentrated in vacuo. The residue was stirred with 2N NaOH (3 mL) for 30 min and then acidified with 2N HCl. The resulting precipitate was extracted into EtOAc and the organic layer was washed with water, dried over sodium sulfate and concentrated *in vacuo*. The residue obtained was triturated with a 1:1 mixture of ether and hexane to give the desired carboxylic acid (0.23g, 78%) as a cream colored solid.

^{1}H NMR ($CDCl_3$) (δ, ppm): 8.97 (d, J=5.5 Hz, 1H), 8.28 (m, 1H), 8.18 (q, J=4.5, 7.0 Hz, 1H,), 7.86 (d, J=5.5 Hz, 1H), 7.52 (m, 1H), 7.46 (t, J=7.0 Hz, 1H), 7.38 (t, J=9.0 Hz, 1H), 7.26 (t, J=9.0 Hz, 1H).

MS(ESI): m/e 361.1 $(M+1)^+$

EXAMPLE 38



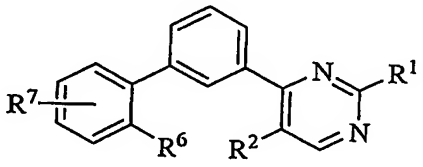
To a solution of the carboxylic acid (0.18 g, 0.5 mmol), from Example 37, in dry DMF (2 mL) was added CDI (0.1g, 0.62 mmol), and the mixture was stirred at room temperature for 1h. Solid dry ammonium acetate (0.5g, 6.5 mmol) was then added and the mixture was stirred at room temperature overnight. The reaction was quenched with water (~10 mL) and extracted with EtOAc. The organic phase was washed with water, dried over sodium sulphate and concentrated *in vacuo*. The crude product obtained was purified on silica-gel by radial chromatography using 75% EtOAc in hexane to yield the pure product (0.08g , 44%) as a cream colored solid.

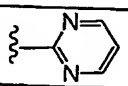
^{1}H NMR ($CDCl_3$) (δ, ppm): 8.89 (d, J=5.5 Hz, 1H), 8.18 (m, 1H), 8.13 (m, 1H,), 7.88 (bs, 1H), 7.79 (d, J=5.5 Hz, 1H), 7.45 (m, 1H), 7.43 (m, 1H), 7.31 (t, J=9.0 Hz, 1H), 7.18 (t, J=9.0 Hz, 1H), 6.60 (bs, 1H).

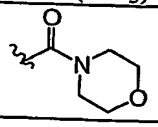
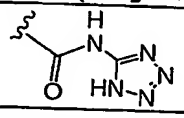
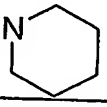
MS(ESI): m/e 360.1 $(M+1)^+$.

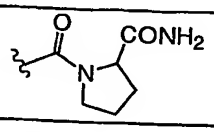
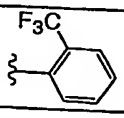
Further Examples of this invention are described in **TABLE 4.** These compounds were prepared employing the chemistry similar to that described in Examples 36-38.

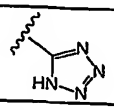
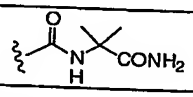
TABLE 4

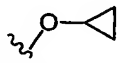
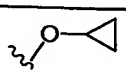
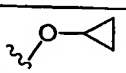


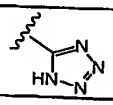
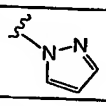
EXAMPLE #	R^6	R^7	R^2	R^1	MS (m/e, M+1)
39	OCF_3	H	H	H	317
40	OCF_3	H	H		395
41	OCF_3	H	H	$-SCH_3$	363
42	OCF_3	H	H	$-SO_2CH_3$	395

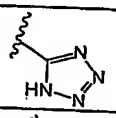
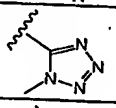
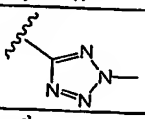
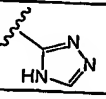
EXAMPLE #	R^6	R^7	R^2	R^1	MS (m/e, M+1)
43	OCF_3	H	H	$-SOCH_3$	379
44	OCF_3	H	H	NH_2	332
45	OCF_3	H	H	$NHSO_2CH_3$	410
46	OCF_3	H	H	$N(SO_2CH_3)_2$	488
47	OCF_3	H	H	$NHCO(CH_3)_3$	416
48	OCF_3	H	H	$CON(CH_3)OCH_3$	404
49	OCF_3	H	H		430
50	OCF_3	H	H	CH_3CO	359
51	OCF_3	H	H	$CONHC(CH_3)_2COOCH_3$	460
52	OCF_3	H	H	$CONHCH_2CH_2CN$	413
53	OCF_3	H	H	$CONHC(CH_3)_2COOH$	446
54	OCF_3	H	H	$CONHC(CH_3)_2CONH2$	445
55	OCF_3	H	H	$CON(CH_2CH_2)_2NH$	429
56	OCF_3	H	H		428
57	OCF_3	H	H	$CONHC(CH_2)_2COOCH_3$	458
58	OCF_3	H	H	$CONHC(CH_2)_2COOH$	444
59	OCF_3	H	H	$CONHC(CH_2)_2CONH_2$	443
60	OCF_3	H	H	$CON(CH_2)_2N(CH_3)_2$	431
61	OCF_3	H	H	$CONHCH_3$	373
62	OCF_3	H	H	$CON(CH_3)_2$	388
63	OCF_3	H	H	$COOCH_3$	375
64	OCF_3	H	H	$CONHCH(CH_3)CONH_2$ (S)	431
65	OCF_3	H	H	$CON(CH_2)_2$ 	471
66	OCF_3	H	H	$CONHC(CH_3)_3$	416

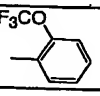
EXAMPLE #	R^6	R^7	R^2	R^1	MS (m/e, M+1)
67	OCF_3	H	H	$CON(CH_3)_2CH_2OH$	431
68	OCF_3	H	H	$CONHC(CH_3)CONH_2$ (R)	431
69	OCF_3	H	H		457
70	OCF_3	H	CH_3	CH_3	345
71	OCF_3	H	CH_3	COOH	375
72	OCF_3	H	CH_3	$CONH_2$	374
73	OCF_3	H	H	$CONHCH_2CONH_2$	417
74	OCF_3	H	Cl	CH_3	365 & 367
75	OCF_3	H	Cl	$CONH_2$	394 & 396
76	OCF_3	H	H	$NHCONH_2$	409
77	CF_3	H	H	CH_3	315
78	CF_3	H	H	H	301
79	CF_3	H	H	COOH	345
80	CF_3	H	H	$CONH_2$	344
81	CF_3	H	H		445
82	CF_3	H	H	SH	333
83	CF_3	H	H	$S\text{-}COCH_3$	375
84	CF_3	H	H	Cl	335 & 337
85	CF_3	H	H	CN	326

EXAMPLE #	R^6	R^7	R^2	R^1	MS (m/e, M+1)
86	CF_3	H	H		369
87	CF_3	5-F	H	CH_3	333
88	CF_3	5-F	H	COOH	363
89	CF_3	5-F	H	$CONH_2$	362
90	CF_3	4-CF_3	H	CH_3	383
91	CF_3	4-CF_3	H	COOH	413
92	CF_3	4-CF_3	H	$CONH_2$	412
93	CF_3	4-CF_3	H		497
94	O-Ph	H	H	CH_3	339
95	O-Ph	H	H	COOH	369
96	O-Ph	H	H	$CONH_2$	368
97	H	O-Ph	H	$CONH_2$	368
98	Cl	H	H	CH_3	281
99	H	3-Cl	H	CH_3	281
100	-SO_2NH-tBu	H	H	CH_3	382
101	-SO_2NH_2	H	H	CH_3	326
102	-CONH-tBu	H	H	CH_3	346
103	-$CONH_2$	H	H	CH_3	290
104	-CONH-tBu	H	H	COOH	376

EXAMPLE #	R^6	R^7	R^2	R^1	MS (m/e, M+1)
105	-CONH-tBu	H	H	$CONH_2$	375
106	Cl	3-Cl	H	COOH	344
107	Cl	3-Cl	H	$CONH_2$	343
108	Cl	3-Cl	H	$COOCH_3$	359
109	$-SO_2NH$-tBu	H	H	COOH	412
110	$-SO_2NH_2$	H	H	COOH	356
111	$-SO_2NH$-tBu	H	H	$CONH_2$	411
112	$-SO_2NH_2$	H	H	$CONH_2$	355
113	OtBu	H	H	CH_3	319
114	OtBu	H	H	COOH	349
115	OtBu	H	H	$CONH_2$	348
116		H	H	CH_3	303
117		H	H	COOH	333
118		H	H	$CONH_2$	332
119	OCH_2CF_3	H	H	CH_3	345
120	OCH_2CF_3	H	H	COOH	375
121	OCH_2CF_3	H	H	$CONH_2$	374
122	CHO	H	H	$CONH_2$	304
123	H	$3\text{-}CF_3$	H	$CONH_2$	344

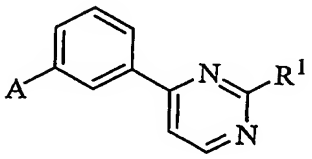
EXAMPLE #	R^6	R^7	R^2	R^1	MS (m/e, M+1)
124	H	4-CF_3	H	$CONH_2$	344
125	H	3-F	H	$CONH_2$	294
126	H	4-Cl	H	$CONH_2$	310
127	H	4-F	H	$CONH_2$	294
128		H	H	$CONH_2$	344
129	OCH_3	3-OCH_3	H	$CONH_2$	336
130	OCH_3	5-Cl	H	$CONH_2$	340
131	CH_3	H	H	$CONH_2$	290
132	CH_3	3-F	H	$CONH_2$	308
133		H	H	$CONH_2$	342
134	H	4-(CH_2OH)	H	$CONH_2$	306
135	H	3-Cl	H	$CONH_2$	310
136	H	3-OEt	H	$CONH_2$	320
137	H	4-OEt	H	$CONH_2$	320
138	F	H	H	$CONH_2$	294
139	CH_3	6-CH_3	H	$CONH_2$	304
140	H	4-tBu	H	$CONH_2$	332
141	H	4-OCF_3	H	$CONH_2$	360
142	H	4-$COCH_3$	H	$CONH_2$	318
143	H	3-$COCH_3$	H	$CONH_2$	318

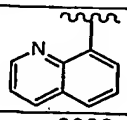
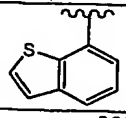
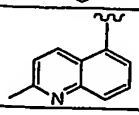
EXAMPLE #	R^6	R^7	R^2	R^1	MS (m/e, M+1)
144	H	3-(CH_2OH)	H	$CONH_2$	306
145	H	4-CN	H	$CONH_2$	301
146	H	3-OCF_3	H	$CONH_2$	360
147	F	4-F	H	$CONH_2$	312
148	H	H	H	$CONH_2$	276
149	OCF_3	4-N(Me)SO_2Me	H	CH_3	438
150	OCF_3	4-N(Me)SO_2Me	H	$CONH_2$	467
151	OCF_3	4-NHCO-tBu	H	CH_3	430
152	OCF_3	4-NHCO-tBu	H	COOH	460
153	OCF_3	4-NHCO-tBu	H	$CONH_2$	459
154	OCF_3	H	H		385
155	OCF_3	H	H		399
156	OCF_3	H	H		399
157	OCF_3	H	H		384
158	OCF_3	H	H	-CH_2CONH_2	374
159	OCF_3	H	H	-CH_2CN	356
160	OCF_3	H	H	-SO_2NHtBu	452

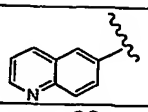
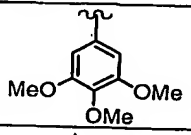
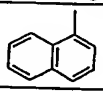
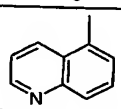
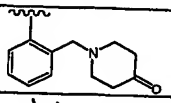
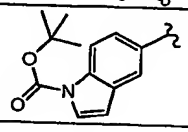
EXAMPLE #	R^6	R^7	R^2	R^1	MS (m/e, M+1)
161	OCF_3	H	H	$-SO_2NH_2$	396
162	OCF_3	H	H	$-SO_2NHMe$	410
163	OCF_3	H	H	$-CH_2OH$	347
164	OCF_3	H	H	-CH(Me)OH	361
165	OCF_3	H	H	$-CH_2NHCOCH_3$	388
166	OCF_3	H	H	$-CH_2OSO_2NH_2$	426
167	OCF_3	H	H	$-NHCH_3$	346
168	OCF_3	H	H	$-NH-CH(CH_3)_2$	374
169	OCF_3	H	H		477

Further Examples of this invention are described in **TABLE 5.**

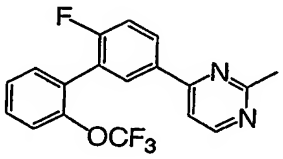
TABLE 5



EXAMPLE #	A	R^1	MS(m/e, M+1)
170		$CONH_2$	328
171		$CONH_2$	332
172		$CONH_2$	343

173		$CONH_2$	328
174		$CONH_2$	366
175		$CONH_2$	328
176		$CONH_2$	329
177		$CONH_2$	387
178		$CONH_2$	415

EXAMPLE 179



5

Step A: Preparation of 2-methyl-4-(3-bromo-4-fluoro phenyl)-pyrimidine

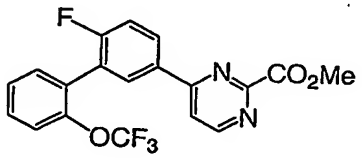
To the solution of 3-bromo-4-fluoroacetophenone (434mg, 2mmol) in DMF (5mL) was added N, N-dimethyl formamide dimethyl acetal (0.41mL, 3mmol). The resulting solution was stirred at room temperature overnight. After removal of the solvent and excess reagent, the residue was dissolved in anhydrous THF, and teated with aged acetamidine in THF suspension (a mixture of acetamidine hydrochloride (283mg, 3mmol) and potassium t-butoxide (336mg, 3mmol) in THF (10mL), reflux 1 hour). The orange suspension was then refluxed overnight. After cooling to room temperature, the reaction mixture was diluted in water, and extracted with EtOAc (3 times). The combined organic layer was washed with brine, and dried over anhydrous sodium sulfate. After concentration, the crude product was applied to column chromatographyon silica gel to afford the final product as a yellow solid, 400 mg, 75% yield. The above product was used for the Suzuki coupling in the next step.

Step B: Coupling of 2-methyl-4-(3-bromo-4-fluorophenyl)-pyrimidine with 2-trifluoromethoxyphenyl boronic acid

To the solution of 2-trifluoromethoxyphenyl boronic acid (216mg, 1.05mmol) and the bromophenyl compound (200mg, 11.6mmol) in n-propanol (5mL) was added palladium acetate (35mg, 0.15mmol), triphenyl phosphine (118mg, 0.45mmol), and aqueous sodium carbonate (2.0M, 0.45mL, 0.9mmol). The reaction mixture was stirred at 90°C for 16 hours. After cooling to room temperature, the mixture was filtered through a Celite pad, and washed with ethyl acetate (3 times). The filtrate was concentrated. The resulting residue was dissolved in ethyl acetate and washed with saturated sodium carbonate aqueous solution and brine, the organic layer was dried over anhydrous sodium sulfate. After concentration, the crude product was applied to column chromatographyon silica gel to afford the final the titled compound, as a white solid. ^{1}H NMR ($CDCl_3$) (δ, ppm): 8.70 (d, J=5.0 Hz, 1H), 8.18 (m, 1H), 8.11 (q, J=4.5, 7.0 Hz, 1H), 7.50 (m, 3H), 7.45 (t, J=3.0 Hz, 1H), 7.34 (t, J=9.0 Hz, 1H), 7.22 (t, J=9.0 Hz, 1H), 2.82 (s, 1H).

MS (ESI): m/e 349 $(M+1)^+$

EXAMPLE 180

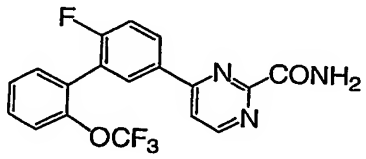


To the solution of 2-methylpyrimidine(from Example 179) (70mg, 0.21mmol) in pyridine (3ml) was added selenium dioxide (117mg, 1.1mmol). The resulting yellow solution was refluxed for 20 hours. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and 2N HCl. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine and dried over anhydrous sodium sulfate. The crude acid was dissolved in methanol, and treated with excess 2.0M trimethylsilyldiazomethane in methanol solution at room temperature for 10 minutes. After concentration, the titled compound was isolated via column chromatography on silica gel, as a yellow solid.

^{1}H NMR ($CDCl_3$) (δ, ppm): 8.97 (d, J=5.5 Hz, 1H), 8.28 (m, 1H), 8.18 (q, J=4.5, 7.0 Hz, 1H,), 7.86 (d, J=5.5 Hz, 1H), 7.52 (m, 1H), 7.46 (t, J=7.0 Hz, 1H), 7.38 (t, J=9.0 Hz, 1H), 7.26 (t, J=9.0 Hz, 1H), 4.12 (s, 1H).

MS (ESI): m/e 393 (M+1)

EXAMPLE 181



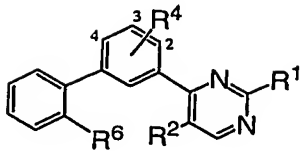
The pyrimidine methyl ester (from Example 180) (120mg, 0.31mmol) in ammonium-methanol (2.0M, 3mL), was stirred at 70°C in a sealed tube. The reaction was stirred at that temperature for overnight. After cooling down, the reaction mixture was concentrated to give the titled compound as yellow foam.

^{1}H NMR ($CDCl_3$) (δ, ppm): 8.89 (d, J=5.5 Hz, 1H), 8.18 (m, 1H), 8.13 (m, 1H,), 7.88 (bs, 1H), 7.79 (d, J=5.5 Hz, 1H), 7.45 (m, 1H), 7.43 (m, 1H), 7.31 (t, J=9.0 Hz, 1H), 7.18 (t, J=9.0 Hz, 1H), 6.60 (bs, 1H).

MS (ESI): m/e 378 $(M+1)^+$

Further Examples of this invention are shown below in **TABLE 6**.

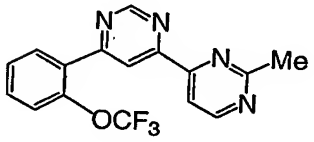
TABLE 6



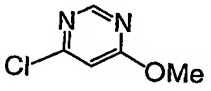
EXAMPLE #	R^6	R^4	R^2	R^1	MS (m/e, M+1)
182	OCF_3	4-F	H	CH_3	349
183	OCF_3	4-F	H	COOH	379
184	OCF_3	4-F	H	$COOCH_3$	393
185	OCF_3	4-F	H	$CONH_2$	378
186	CF_3	4-F	H	$COOCH_3$	377
187	CF_3	4-F	H	$CONH_2$	362
188	CF_3	4-F	H	CH_3	351
189	OCF_3	2-OCH_2Ph	H	CH_3	437
190	OCF_3	2-OH	H	CH_3	347
191	OCF_3	4-NHAc	H	CH_3	386
192	OCF_3	4-NHAc	H	$COOCH_3$	432
193	OCF_3	4-NHAc	H	$CONH_2$	417
194	OCF_3	2-F	H	CH_3	349
195	OCF_3	2-F	H	$COOCH_3$	393
196	OCF_3	2-F	H	$CONH_2$	378
197	OCF_3	4-Br	H	CH_3	410
198	OCF_3	4-Br	H	$COOCH_3$	454
199	OCF_3	4-Br	H	$CONH_2$	439
200	OCF_3	4-Br	H	COOH	440
201	OCF_3	4-Ph	H	CH_3	407
202	OCF_3	4-Ph	H	$COOCH_3$	451
203	OCF_3	4-Ph	H	$CONH_2$	436
204	OCF_3	4-Cl	H	CH_3	365
205	OCF_3	4-Cl	H	$COOCH_3$	409

EXAMPLE #	R^6	R^4	R^2	R^1	MS (m/e, M+1)
206	OCF_3	4-Cl	H	COOH	395
207	OCF_3	4-Cl	H	$CONH_2$	394
208	OCF_3	2-Cl	H	CH_3	365
209	OCF_3	2-Cl	H	$COOCH_3$	409
210	OCF_3	2-Cl	H	$CONH_2$	394
211	OCH_2CF_3	4-F	H	CH_3	363
212	OCH_2CF_3	4-F	H	$COOCH_3$	407
213	OCH_2CF_3	4-F	H	COOH	393
214	OCH_2CF_3	4-F	H	$CONH_2$	392
215	H	4-OCH_2CF_3	H	$CONH_2$	373
216	F	4-OCH_2CF_3	H	$CONH_2$	392

EXAMPLE 217



Step 1A: Preparation of 4-chloro-6-methoxypyrimidine

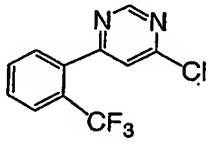


To the solution of 4,6-dichloropyrimidine (2g, 13.4mmol) in methanol (20mL), was added sodium methoxide (25%w/w, 3.1mL, 13.4mmol). The white precipitate was formed immediately. 30 minutes later the reaction mixture was filtrated through a Celite pad, the filter cake was washed with ethyl acetate. The filtrate was then concentrated, and applied to column chromatoghraphy on silica gel to afford the titled compound as a white crystalline solid.

Step 1B: Coupling of 4-chloro-6-methoxypyrimidine with 2-trifluoromethoxyphenylboronic acid

To the solution of 2-trifluoromethylphenyl boronic acid (1.74g, 9.1mmol) and the 4-chloro-6-methoxypyrimidine (940mg, 6.5mmol) in n-propanol (15mL) was added palladium acetate (292mg, 1.3mmol), triphenyl phosphine (1g, 4mmol), and aqueous sodium carbonate (2.0M, 4mL, 7.8mmol). The reaction mixture was stirred at 90°C for 16 hours. After cooling to room temperature, the mixture was filtered through a Celite pad, and washed with ethyl acetate (3 times). The filtrate was concentrated. The resulting residue was dissolved in ethyl acetate, and washed with saturated sodium carbonate aqueous solution and brine. The organic layer was dried over anhydrous sodium sulfate. After concentration, the crude product was applied to column chromatographyon silica gel to afford the titled compound as yellow oil.
^{1}H NMR ($CDCl_3$) (δ, ppm): 8.83 (s, 1H), 7.75 (d, J=8.0 Hz, 1H,), 7.61 (t, J=8.0 Hz, 1H), 7.54 (t, J=7.5 Hz, 1H), 7.45 (t, J=7.5 Hz, 1H), 6.83 (s, 1H), 4.02 (s, 1H).
MS (ESI): m/e 255 $(M+1)^+$

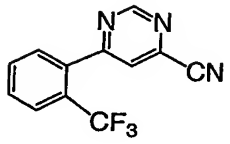
Step 2: Preparation of



To the solution of the 4-(2-trifluoromethylbenzene)-6-methoxypyrimidine (from Step B of Step 1) (45mg, 0.18mmol) in acetic acid (1.5mL) was added HBr (0.5mL). The resulting colorless solution was stirred at 80°C for 1 hour. After cooling to room temperature, the solvent was removed under reduced pressure, the residue was partitioned between ethyl acetate and saturated sodium bicarbonate aqueous solution. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, and dried over anhydrous sodium sulfate. The crude product was used immediately for the next step. The above pyrimidone was dissolved in $POCl_3$ (5mL). The reaction mixture was refluxed for 30 minutes. After removing the solvent, the residue was partitioned between ethyl acetate and saturated sodium bicarbonate aqueous solution. The combined organic layer was washed with brine, and dried over anhydrous sodium sulfate. The titled compound was isolated via column chromatography on silica gel, as a yellow solid.

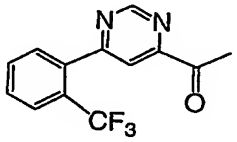
^{1}HNMR ($CDCL_3$) (δ, ppm): 9.06 (s, 1H), 7.80(d, J=4.0 Hz, 1H), 7.75 (t, J=8.0 Hz, 1H), 7.61 (t, J=7.5 Hz, 1H), 7.45 (t, J=7.0 Hz, 1H), 7.24 (s, 1H).
MS (ESI): m/e 259 $(M+1)^+$

Step 3: Preparation of



To the solution of the chloropyrimidine (from Step 2) (300mg, 1.2mmol) in DMF (5mL), was added potassium cyanide (117mg, 1.7mmol) and p-tosylate sodium salt (83mg, 0.46mmol). The resulting mixture was stirred at 80°C for 2 hours. After cooling to room temperature, and removing the solvent under reduced pressure, the residue was partitioned between ethyl acetate and water. The aqueous was extracted with ethyl acetate, the organic layer was washed with brine, and dried over anhydrous sodium sulfate. After concentration, the titled compound was collected as a yellow solid.
^{1}H NMR ($CDCl_3$) (δ, ppm): 9.41 (s, 1H), 7.83 (d, J=7.5 Hz, 1H), 7.78 (s, 1H), 7.70-7.64 (m, 2H), 7.50 (d, J=7.5 Hz, 1H).
MS (ESI): m/e 250 $(M+1)^+$

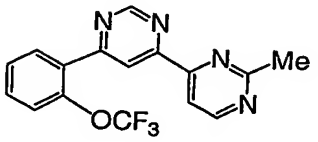
Step 4: Preparation of



To the solution of the cyano compound(from Step 3) (160mg, 0.64mmol) in dry ether (5mL) was added dropwise, at –78°C, the methyl magnesium bromide in ether solution (3.0m, 0.64mL, 1.9mmol). The reaction mixture was stirred at –78°C for 1 hour, and at room temperature for another 1 hour. The reaction mixture was partitioned between ether and water. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, and dried over anhydrous sodium sulfate. After concentration, the titled compound was collected as a yellow solid.

^{1}HNMR ($CDCL_3$) (δ, ppm): 9.41 (s, 1H), 8.02 (s, 1H), 7.81 (d, J=7.0 Hz, 1H), 7.65 (d, J=7.0 Hz, 1H), 7.61 (d, J=7.0 Hz, 1H), 7.48 (d, J=7.0 Hz, 1H), 2.76 (s, 1H).
MS (ESI): M/E 267 $(M+1)^+$

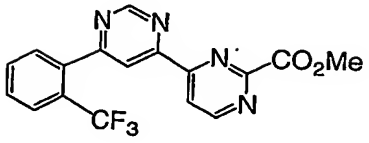
Step 5: Preparation of



To the solution of methylketone (from Step 4) (50mg, 0.19mmol) in DMF (2mL) was added N, N-dimethyl formamide dimethyl acetal (0.034mL, 0.28mmol). The resulting solution was stirred at room temperature for overnight. After removal of the solvent and excess reagent, the residue was dissolved in anhydrous THF, and teated with aged acetamidine in THF suspension (a mixture of acetamidine hydrochloride (26mg, 0.28mmol) and potassium t-butoxide (32mg, 0.28mmol) in THF (5mL), reflux 1 hour). The orange suspension was then refluxed for overnight. After cooling to room temperature, the reaction mixture was diluted in water, and extracted with EtOAc (3 times). The combined organic layer was washed with brine, and dried over anhydrous sodium sulfate. After concentration, the crude product was applied to column chromatography on silica gel to afford the titled compound as a yellowish solid.
^{1}HNMR ($CDCL_3$) (δ, ppm): 9.38 (s, 1H), 8.86 (d, J=5.5 Hz, 1H), 8.58 (s, 1H), 8.25 (d, J=5.5 Hz, 1H), 7.82 (d, J=8.0 Hz, 1H), 7.68 (t, J=7.5 Hz, 1H), 7.59 (t, J=7.5 Hz, 1H), 7.55 (d, J=5.5 Hz, 1H), 2.80 (s, 1H).

MS (ESI): M/E 317 $(M+1)^+$

EXAMPLE 218

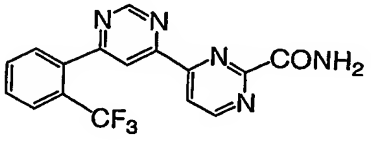


To the solution of methylpyrimidine (form Example 217, Step 5) (50mg, 0.15mmol) in pyridine (2mL), was added selenium dioxide (166mg, 1.5mmol). The resulting yellow solution was refluxed for 20 hours. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and 2N HCl. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, and dried over anhydrous sodium sulfate. The crude acid was dissolved in MeOH, and treated with excess 2.0M trimethylsilyldiazomethane in methanol solution at room temperature for 10 minutes. After concentration, the titled compound was isolated via column chromatography on silica gel, as a yellow solid.

^{1}HNMR ($CDCL_3$) (δ, ppm): 9.45 (s, 1H), 9.18 (d, J=5.0 Hz, 1H), 8.68 (m, 2H), 7.83 (d, J=8.0 Hz, 1H), 7.68 (t, J=7.5 Hz, 1H), 7.55 (t, J=7.5 Hz, 1H), 7.54 (d, J=5.5 Hz, 1H), 4.06 (s, 1H).

MS (ESI): m/e 361 $(M+1)^+$

EXAMPLE 219



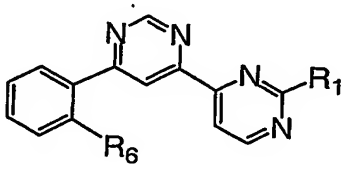
The pyrimidine methyl ester (from Example 218) (14mg, 0.04mmol) in ammonium-methanol (2.0M, 2mL), was stirred at 70°C in a sealed tube. The reaction was stirred at that temperature for overnight. After cooling down, the reaction mixture was concentrated to give the titled compound as yellow foam.

^{1}HNMR ($CDCL_3$) (δ, ppm): 9.39 (s, 1H), 9.10 (d, J=5.0 Hz, 1H), 8.60 (s, 1H), 8.57 (d, J=5.0 Hz, 1H), 7.86 (bs, 1H), 7.77 (d, J=8.0 Hz, 1H), 7.64 (t, J=7.5 Hz, 1H), 7.58 (t, J=7.5 Hz, 1H), 7.52 (d, J=5.5 Hz, 1H), 6.94 (bs, 1H).

MS (ESI): M/E 346 $(M+1)^+$.

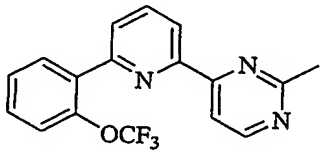
Further Examples of this invention were synthesized using the same procedures described in Examples 217-219 and are summarized in TABLE 7.

TABLE 7

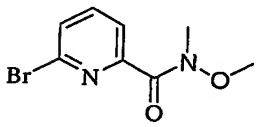


EXAMPLE #	R_6	R_1	MS (m/e, M+1)
220	OCF_3	CH_3	333
221	OCF_3	COOH	363
222	OCF_3	$CONH_2$	362

EXAMPLE 223



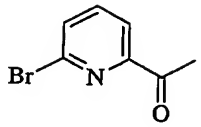
Step 1: Preparation of



To a solution of 6-bromopicolinic acid (2.0g) in anhydrous DMF (10 mL) was added carbonyl diimidazole (2.4g), and the solution was stirred at room temperature for 1 hour. N,O-dimethylhydroxyl- amine hydrochloride (1.5g) was then added and the reaction was stirred overnight at room temperature. The reaction, after quenching with water (30 mL), was extracted with 2 x 20 ml portions of EtOAc. The organic phase was dried over sodium sulfate and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel using 50% EtOAc in hexanes to give the pure amide.

^{1}HNMR ($CDCL_3$) (δ, ppm): 7.70-7.61 (m, 2H), 7.59 (t, J=7.5 Hz, 1H), 3.85 (s, 3H), 3.4 (s, 3H).
MS: m/e 245/247 $(M+1)^+$

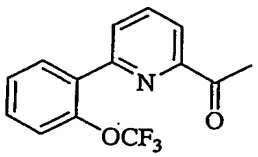
Step 2: Preparation of



A solution of the amide (from Step 1) (2.3g) in anhydrous THF (~3ml) was cooled to 0 °C, and methylmagnesiumchloride (9.4ml) was added. After stirring for 1h at 0 °C, the reaction was poured into 5% HCl in ethanol, and the mixture was partitioned between brine and a 1:1 ether and methylene chloride. The organic phase was separated and dried over sodium sulfate and concentrated *in vacuo*. The material was used in the next step without any purification.

^{1}HNMR ($CDCL_3$) (δ, ppm): 8.03 (dd, J_1=1.2 Hz and J_2=7.0 Hz, 1H), 7.72 (m, 2H), 2.74 (s, 3H).
MS: m/e 200/2 $(M+1)^+$

Step 3: Preparation of

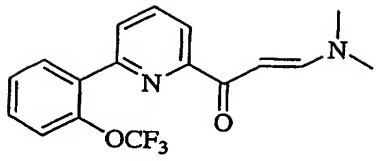


To a solution of the ketone (from step 2) (0.8g) in a mixture of toluene (15 mL), 8ml of ethanol (8 mL), and deionized water (8 mL) was added 2-trifluoromethoxyphenylboronic acid (0.824g) under N_2. Sodium carbonate (0.848g) was added to the solution followed by tetrakistriphenylphosphine palladium (0.231g). The reaction was refluxed for 2h, cooled to room temperature and partitioned between EtOAc and water. The aqueous layer was extracted a second time with EtOAc. The combined organic phase was dried over sodium sulfate and concentrated *in vacuo*. The crude material obtained was purified by column chromatography on silica gel using 15% EtOAc in hexanes to yield the pure ketone.

^{1}HNMR ($CDCL_3$) (δ, ppm): 8.03 (dd, 1H), 7.93 (dd, 1H), 7.88 (d, 1H), 7.87 (s, 1H, 7.45 (m, 2H), 7.39 (m, 1H), 2.78 (s, 3H).

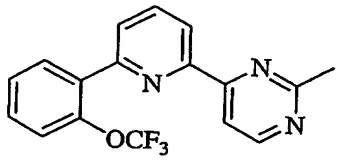
MS: m/e 282 $(M+1)^+$

Step 4: Preparation of



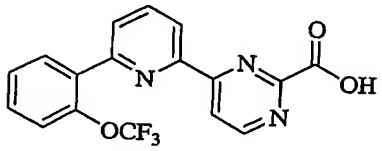
To a solution of the ketone from Step 3 (0.96g) in DMF (3.5 mL) was added N,N-dimethylformamide dimethyl acetal (0.44g), and the mixture was stirred at 150°C for 18h. The reaction was then cooled to room temperature and partitioned between EtOAc and water. The aqueous layer was extracted a second time with EtOAc. The combined organic phase was dried over sodium sulfate and concentrated *in vacuo*. The crude material obtained was used in the next step without purification.
MS: m/e 337 $(M+1)^+$

Step 5: Preparation of



Acetamidine hydrochloride (0.51g), anhydrous DMF (2ml) and potassium t-butoxide (0.605g) were placed in a 5ml-microwave reaction tube fitted with a stirbar. A solution of the product from step 4 (1.2g) in anhydrous DMF (2 mL) was added to the content in tube. The reaction vessel was sealed and heated 140 °C for 20 min. The microwave tube was cooled, and the reaction was partitioned between EtOAc and water. The organic phase was washed with water, dried over sodium sulfate and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel using 25% EtOAc in hexanes.
^{1}HNMR ($CDCL_3$) (δ, ppm): 8.78 (d, J= 5.3 Hz, 1H), 8.52 (dd, J=0.9 Hz and 7.8 Hz. 1H), 8.28 (d, J=5.0 Hz, 1H), 7.92-7.98 (m, 2H), 7.80 (dd, J=0.9 Hz and 7.8 Hz. 1H), 7.42-7.5 (m, 2H), 7.38-7.43 (m, 1H), 2.85 (s, 3H).
MS: m/e 332 $(M+1)^+$

EXAMPLE 224

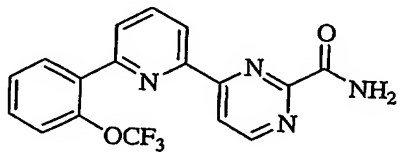


A mixture of the methyl pyrimidine, from Example 223, (0.4g), SeO2 (2.0g) and anhydrous pyridine (16 mL) was refluxed overnight. The reaction was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue obtained was dissolved in EtOAc and washed with 1 N HCl. The organic phase, after drying over sodium sulfate, was concentrated *in vacuo*. The crude product was purified by reverse-phase column chromatography using CH3CN-water containing 0.1% TFA to give the desired product.

NMR (CDCl3):

MS: m/e 362 $(M+1)^+$

EXAMPLE 225

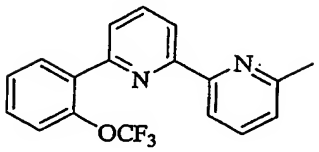


To a solution of the acid (from Example 215) (0.2g) in anhydrous DMF (1mL) was added carbonyldiimidazole (0.178g), and the solution was stirred at room temperature for 1 hour. Anhydrous ammonium acetate (0.17g) was then added and the reaction was stirred overnight. The reaction was poured into water (10mL) and extracted with EtOAc. The organic phase was dried over sodium sulfate and concentrated *in vacuo*. The crude product obtained was purified by column chromatography on silica gel using 100% EtOAc in hexanes to give the pure amide.

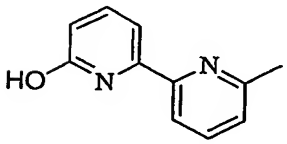
NMR(CDCl3):

MS: m/e 361 $(M+1)^+$

EXAMPLE 226



Step 1: Preparation of

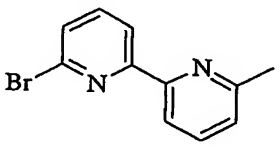


To a solution of 6-methyl-2, 2'-dipyridyl (1.0g) in CH_3CN (12 mL) was added iodomethane (5.0g) and the reaction refluxed for two days. The reaction was cooled to room temperature and filtered. The filtrate was diluted with ether, and the precipitate formed (mono-methylated desired product) was filtered, washed with ether and dried *in vacuo*.

To a cold solution of potassium ferricyanide (III) (4.4g) in water (22ml) were added cold solutions of sodium hydroxide (4.5g) (in water (17.5ml)) and the above solid (1.04g) (in water (17.5ml)). The reaction was kept at 5° C for 4 hours and then extracted with dichloromethane. The product was purified by column chromatography on silica gel using 20% methanol in EtOAc.

MS: m/e 201 $(M+1)^+$

Step 2: Preparation of

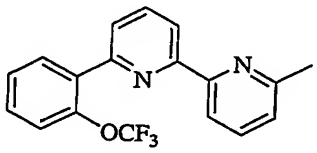


To a mixture of triphenylphosphine (0.682g) and dry acetonitrile (7ml) was added Br_2 (0.384g) dropwise under stirring at 0° C. The resulting mixture was stirred at ambient for 1h and then cooled down to 0° C. A solution of the compound from Step 1 in anhydrous acetonitrile (2 mL) was added to the reaction and refluxed overnight. The reaction was cooled, poured over

ice and filtered. The filtrate was neutralized with 10% sodium carbonate solution and extracted with dichloromethane. The organic phase was dried over sodium sulfate and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel using 5% EtOAc in hexanes.

MS: m/e 249/251 $(M+1)^+$

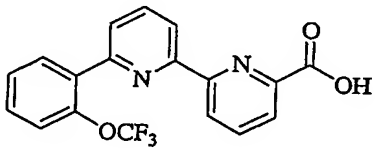
Step 3: Preparation of



To a mixture of the bromo compound, from Step 2, (0.067g) and 2-trifluoromethoxyphenyl boronic acid (0.167g), anhydrous toluene (0.5mL) and potassium fluoride (0.031g) were added triphenylphosphine (0.007g) and palladium acetate (0.003g) under N_2. The reaction was refluxed for 3h, cooled and partitioned between EtOAc and water. The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The crude material obtained was purified by column chromatography on silica gel using a gradient of 12-15% EtOAc in hexanes to yield the pure product.

MS: m/e 331 $(M+1)^+$

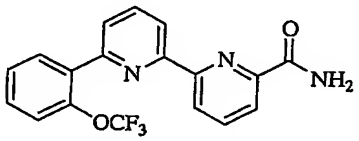
EXAMPLE 227



A solution of the methyl pyridine (from Step 3 of Example 226) (0.068g) in anhydrous pyridine (3 mL) was treated with selenium dioxide (0.4g). The reaction was refluxed overnight. The reaction was cooled, filtered through Celite and concentrated. The residue

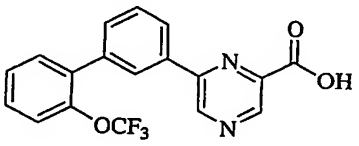
dissolved EtOAc, washed with 1 N HCl and water. The organic phase was dried over sodium sulfate and concentrated. The product obtained was carried forward to the next step.
MS: m/e 361 $(M+1)^+$

EXAMPLE 228

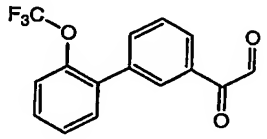


The titled compound was prepared from the acid obtained in Example 227 using the procedure described in Example 216. The crude material was purified by column chromatography on silica gel using 50% EtOAc in hexanes to give the pure amide.
^{1}H NMR ($CDCl_3$): 5.88 (s, 1H), 7.44 (d, J=7.6 Hz, 1H), 7.47-7.55 (m, 2H), 7.80 (d, J=7.8 Hz, 1H), 7.96-8.07 (m, 4H), 8.30 (d, J=7.8 Hz, 1H), 8.44 (d, J=8.0 Hz, 1H), 8.75 (d, J=8.0 Hz, 1H)
MS: m/e 360 $(M+1)^+$

EXAMPLE 229



<u>Step 1</u>: Preparation of



A mixture of selenium dioxide (1.50g), dioxane (6mL) and deionized water (0.25 mL) was stirred at 50° C for 15 minutes to dissolve the selenium dioxide, and then the methyl ketone (from Example 217, Step 4)(3.1g) was added in one portion to the reaction and refluxed for six hours. The reaction was cooled and filtered. The filtrate was concentrated in vacuo and the residue (yellow) was diluted in 50% EtOAc in hexanes and washed with saturated sodium

thiosulfate solution until the organic layer was clear. The organic phase was dried over sodium sulfate and concentrated. The crude keto-aldehyde was used in the next step without further purification.

Step 2:

To a solution of the keto-aldehyde (from Step 1) (2.8g) in anhydrous methanol (3.1mL) at -30° C was added a pre-cooled solution of L-alaninamide hydrochloride (1.20g) in anhydrous methanol (6.2ml). A 2M NaOH solution (6.2ml) was then added dropwise, and the mixture was stirred at 0°C for 2h and then 2h at room temperature. The reaction was quenched with 10ml of 1N HCl, then neutralized with ~1g of solid sodium bicarbonate. The solvent was removed *in vacuo* and the residue was extracted with EtOAc. The organic phase was washed with water, dried over sodium sulfate and concentrated to give a mixture of regioisomers of pyrazinones that were not separated and carried to the next step.
MS: m/e 347 $(M+1)^+$

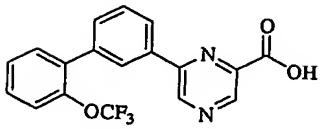
Step 3:

A mixture of the pyrazinone isomers from Step 2 (1.75g) and $POCl_3$ (8 mL) were placed in sealed tube and heated to 170° C for 18 hours. The reaction was concentrated in vacuo and the residue was dissolved in EtOAc. The organic phase was washed with water and saturated sodium bicarbonate solution, then dried over sodium sulfate. The regioisomers were separated by column chromatography on silica gel using a gradient of 5-6% EtOAc in hexanes. The less polar isomer was then taken forward to Step 4 described below.
MS: m/e 365 $(M+1)^+$

Step 4:

To a solution of the chloropyrazine (from Step 3) (0.31g) in EtOH (3 mL) were added sodium acetate (77mg) and 10% (w/w) palladium on carbon (0.1g). The reaction was shaken under 45 pounds of hydrogen gas for four hours. After that period, the reaction aws filtered through a pad of Celite and the filtrate was *concentrated in vacuo*. The crude product was purified by column chromatography on silica gel using 15% EtOAc in hexanes to give the titled methyl pyrazine compound.
MS: m/e 331 $(M+1)^+$

EXAMPLE 230



To a solution of the methyl pyrazine (from Example 229 Step 4) (0.051g) in anhydrous pyridine (0.3 mL) was added a solution of $nBu_4N^+MnO4^-$ (0.11g) in pyridine (0.3 mL) slowly and the reaction was stirred at room temperature for 30 min. and then at 65° C overnight. Two additional equivalents of tetrabutylammonium permanganate were added the following morning and the reaction was heated for two more hours. The reaction was allowed to cool to room temperature at which point it was quenched with saturated sodium thiosulfate sulfate. The aqueous layer was acidified to pH=1 with 1 N HCl. The aqueous layer was subsequently extracted with two portions of EtOAc. The organics were further washed with 1 N HCl and dried over sodium sulfate. The organic material was concentrated via rotary evaporator. No further purification was attempted.

MS: m/e 361 $(M+1)^+$

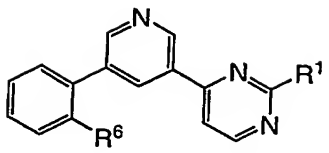
EXAMPLE 231

The acid (54mg) (from Example 230) was dissolved in 200ul of anhydrous DMF and treated with carbonyl diimidazole (49mg) at room temperature for 1 hour. Then, solid ammonium acetate (46mg) was added and the reaction was allowed to continue overnight. The reaction was quenched with ~4ml of H_2O and the aqueous layer extracted with 2 x 4ml portions of EtOAc. The organics were dried over sodium sulfate and concentrated on the rotary evaporator. The crude material was purified by column chromatography on silica gel using 50% EtOAc in hexanes to give the pure amide.

^1H NMR ($CDCl_3$): 6.06(s, 1H), 7.42-7.51 (m, 3H), 7.56 (d, J=7.4 Hz, 1H), 7.66-7.70 (m, 2H), 7.82 (s, 1H), 7.95-8.10 (t, 1H), 8.20 (s, 1H), 9.29 (s, 1H), 9.45 (s, 1H).

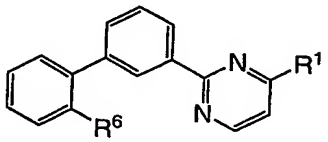
MS: m/e 360 $(M+1)^+$

TABLE 8



EXAMPLE #	R^6	R^1	MS (m/e, M+1)
232	OCF_3	CH_3	332
233	OCF_3	COOH	362
234	OCF_3	$COOCH_3$	376
235	OCF_3	$CONH_2$	361

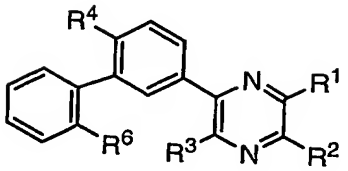
TABLE 9

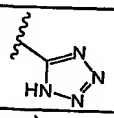
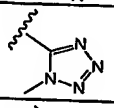
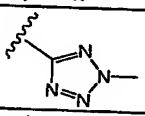
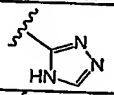
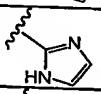
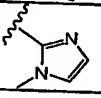


EXAMPLE #	R^6	R^1	MS (m/e, M+1)
236	OCF_3	CH_3	331
237	OCF_3	COOH	361
238	OCF_3	$CONH_2$	360
239	CF_3	CH_3	315
240	CF_3	COOH	345
241	CF_3	$CONH_2$	344

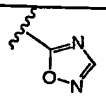
Further examples of pyrazines compounds prepared are listed below..

TABLE 10



EX. #	R^6	R^4	R^3	R^2	R^1	MS: m/e (M+1)
242	OCF_3	H	H	H		385
243	OCF_3	H	H	H		399
244	OCF_3	H	H	H		399
245	OCF_3	H	H	H		384
246	OCF_3	H	H	H		383
247	OCF_3	H	H	H		397
248	OCF_3	H	H	H	$-CH_2CH_2CONH_2$	388
249	OCF_3	H	H	H	$-CH_2CONH_2$	374
250	OCF_3	H	H	H	$-CH_2CN$	356
251	OCF_3	H	H	H	$-SO_2NHtBu$	452
252	OCF_3	H	H	H	$-SO_2NH_2$	396
253	OCF_3	H	H	H	$-SO_2NHMe$	410
254	OCF_3	H	H	H	$-CH_2OH$	347
255	OCF_3	H	H	H	-CH(Me)OH	361

256	OCF_3	H	H	H	$-CH_2NHCOCH_3$	388
257	OCF_3	H	H	H	$-CH_2OSO_2NH_2$	426
258	OCF_3	H	H	H	$-NHCH_3$	346
259	OCF_3	H	H	H	$-NH-CH(CH_3)_2$	374
260	OCF_3	H	H	H	NH_2	332
261	OCF_3	H	H	Cl	$CONH_2$	394
262	OCF_3	H	H	$CONH_2$	Cl	394
263	OCF_3	H	H	H	$CONHNH_2$	375
264	OCF3	H	H	H	$NHSO_2CH_3$	410
265	OCF_3	H	NH_2	NH_2	$CONH_2$	391
266	OCF_3	F	H	H	$CONH_2$	379
267	OCF_3	H	H	CH_3	$OCON(CH_3)_2$	418
268	OCF_3	H	H	$OCON(CH_3)_2$	CH_3	418
269	OCF_3	H	H	$CONH_2$	OCH_3	391
270	OCF_3	H	H	CH_3	$O(CH_2)_2N(CH_3)_2$	418
271	OCF_3	H	H	$O(CH_2)_2N(CH_3)_2$	CH_3	418
272	OCF_3	H	H	CH_3	$NHCH_3$	360
273	OCF_3	H	H	OCH_3	$CONH_2$	391
274	OCF_3	H	H	Cl	CH_3	365
275	OCF_3	H	H	CH_3	H	331
276	OCF_3	H	H	H	CH_3	331
277	OCF_3	H	H	$CONH_2$	H	360

278	OCF_3	F	H	$CONH_2$	H	378
279	OCF_3	H	H	H	SCH_3	363
280	OCF_3	H	H	H	$S(O)CH_3$	379
281	OCF_3	H	H	H	SO_2CH_3	395
282	OCF_3	F	H	H	COOH	379
283	OCF_3	H	H	H	CHO	345
284	OCF_3	H	H	H	$COCH_3$	359
285	OCF_3	H	H	H	CN	342
286	OCF_3	H	H	H	H	316
287	OCF_3	H	H	H		385
288	OCF_3	H	H	H	$CH(OH)CF_3$	414
289	OCF_3	H	H	$CH(OH)CF_3$	H	414
290	OCF_3	H	H	$CONH_2$	OH	376
291	OCF_3	H	H	CH_3	CONH-tBu	415
292	OCF_3	H	H	H	$COCF_3$	412
293	OCF_3	H	H	H	$-OCH_2SO_2NH_2$	426
294	OCF_3	H	H	H	$-CH=CHCO_2CH_3$	401
295	OCF_3	H	H	H	$-CH(NH_2)CH_2CONH_2$	403
296	OCF_3	H	H	$CONH_2$	OCH_3	391
297	OCF_3	H	H	H	$-CONHCH(CH_3)CONH_2$	431
298	OCF_3	H	H	H	$-CON(CH_3)_2$	388

299	OCF_3	H	H	H	$-O(CH_2)_2N(CH_3)_2$	404
300	OCF_3	H	H	H	$-CH_2NHCOCH_3$	388
301	CF_3	H	H	H	$COOCH_3$	359
302	OCF_3	H	H	H	$S-COCH_3$	375
303	CF_3	H	H	H	$CONH_2$	344
304	OPh	H	H	H	$CONH_2$	368
305	OCF_3	H	H	H	$CONHCH_3$	374
306	OCF_3	H	H	NH_2	$NHCH_3$	361
307	OCF_3	H	H	NH_2	COOPr	403
308	Cl	H	H	H	$COOCH_3$	324
309	OCF_3	H	H	NH_2	$CONH_2$	373
310	Cl	H	H	H	$CONH_2$	310
311	OCF_3	H	H	H	$CSNH_2$	376
312	OCF_3	H	H	CH_3	$CONH_2$	374
313	OCF_3	H	H	OCH_3	$CONH_2$	390
314	OCF_3	H	H	H	$NHCOCH_3$	374
315	OCF_3	H	H	H	$N(COCH_3)_2$	416
316	OCF_3	H	H	CH_3	COOH	375
317	OCF_3	H	H	$CONH_2$	$CONH_2$	403
318	OCF_3	H	H	$CH(CH_3)_2$	$CONH_2$	402
319	OCF_3	H	H	$CONH_2$	$CH(CH_3)_2$	402
320	OCF_3	H	H	$CH(CH_3)_2$	$CONHC(=NH)NH_2$	402

321	OCF_3	H	H	$CH(CH_3)_2$	CONHOH	376
322	OCF_3	H	H	H	$NHCONH_2$	374
323	OCF_3	H	CH_3	H	$CONH_2$	373
324	OCF_3	H	CH_3	$CONH_2$	H	373
325	OCF_3	H	H	H	$NHCH_2CONH_2$	388
326	OCF_3	H	H	H	$NHC(=NH)NH_2$	374
327	OCF_3	H	H	H	$C(=NH)NH_2$	359
328	CF_3	H	H	H	COOH	344
329	OCF_3	H	Cl	H	$CONH_2$	394
330	OCF_3	H	CH_3	COOH	H	374
331	OCF_3	H	CH_3	H	COOH	374
332	OCF_3	H	NH_2	H	$CONH_2$	375
333	OCF_3	H	NH_2	H	COOH	376
334	OCF_3	H	Cl	H	COOH	395
335	OCF_3	H	NH_2	$CONH_2$	H	375
336	OCF_3	H	$CONH_2$	H	$CONH_2$	403
337	OCH_2CF_3	H	H	CH_3	Cl	379
338	OCH_2CF_3	H	H	Cl	CH_3	379
339	OCH_2CF_3	H	H	H	CH_3	345
340	OCH_2CF_3	H	H	CH_3	H	345
341	OCH_2CF_3	H	H	H	$CONH_2$	374
342	OCH_2CF_3	H	H	$CONH_2$	H	374

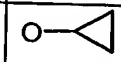
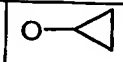
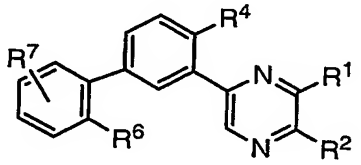
343	OCH_2CF_3	H	H	H	H	331
344	OCH_2CF_3	H	H	H	COOH	375
345	O- 	H	H	H	$COOCH_3$	347
346	O- 	H	H	H	$CONH_2$	332
347	OCF_3	H	H	H	$CONHC(CH_3)_2CONH_2$	445
348	OCF_3	H	H	H	$CH(OH)CH_3$	361
349	OCF_3	H	H	H	$NHSO_2NH_2$	411
350	OCF_3	H	H	H	$N(CH_3)CONH_2$	389
351	OCF_3	H	H	CH_3	$N(CH_3)CONH_2$	403
352	OCF_3	H	H	$N(CH_3)CONH_2$	CH_3	403

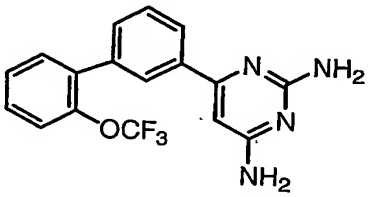
TABLE 11



EX. #	R^6	R^7	R^4	R^2	R^1	MS: m/e (M+1)
353	CF_3	5-F	H	H	$CONH_2$	362
354	CF_3	5-F	H	$CONH_2$	H	362
355	CF_3	4-CF_3	H	H	$CONH_2$	412
356	CF_3	4-CF_3	H	$CONH_2$	H	412
357	OCF_3	H	F	H	$CONH_2$	378

358	OCF_3	H	F	$CONH_2$	H	378
359	CF_3	4-CF_3	H	H	H	369
360	Cl	3-Cl	H	H	$COOCH_3$	358
361	Cl	4-Cl	H	H	$COOCH_3$	358
362	Cl	3-Cl	H	H	$CONH_2$	344
363	Cl	4-Cl	H	H	$CONH_2$	344
364	Cl	6-Cl	H	H	$CONH_2$	344

EXAMPLE 365



A mixture of 2-trifluoromethoxyphenyl boronic acid obtained from Step 1 of Example 36 (0.41g, 2 mMol) and 3-bromophenyl boronic acid (0.4g, 2 mMol) in n-propanol (5 ml) was placed in a microwave reaction tube and stirred at room temperature under N_2 for 15 min. To the resulting solution were then added Ph_3P (0.025g) and $Pd(OAc)_2$ (0.005g) followed by 2M Na_2CO_3 (1.2 mL) and water (0.7 mL). The tube was sealed and the tube was heated in Smith Creator Personal Chemistry Microwave Instrument at 150°C for 900 sec. The reaction was cooled and diluted with water. The mixture was acidified with 1N HCl and extracted with EtOAc. The organic phase was washed with water, dried and concentrated *in vacuo*. The LCMS indicated the desired biphenyl boronic acid, which without further purification was dissolved in a mixture of toluene (1.5 mL) and n-propanol (1.5 mL). The solution was placed in a microwave reaction tube and was added Ph_3P (0.050g) and $Pd(OAc)_2$ (0.005g) followed by 2M Na_2CO_3 (1.2 mL) and water (0.6 mL). The sealed reaction tube was heated in Smith Creator Personal Chemistry Microwave Instrument at 150°C for 1200 sec. The reaction was cooled diluted with water and extracted with EtOAc. The organic phase was washed with water, dried and

concentrated in vacuo. The crude product was purified by radial chromatography using chloroform-methanol-ammonia (10:1:0.1) as the eluent to give the desired product. ^{1}HNMR ($CDCL_3$) (δ, ppm): 8.0 (s, 1H), 7.94 (d, J=7.6 Hz ,1H), 7.5–7.6 (m, 3H), 7.36-7.44 (m, 3H), 6.35 (s, 1H).

MS (ESI): M/E 347 $(M+1)^+$